Protocol I8F-MC-GPIA(a)

Efficacy and Safety of Tirzepatide Once Weekly in Chinese Participants without Type 2 Diabetes Who Have Obesity or are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-CN)

NCT05024032

Approval Date: 25-Aug-2021

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Tirzepatide (LY3298176)

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Protocol Electronically Signed and Approved by Lilly: 10 Jun 2020
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 25-Aug-2021 GMT

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1. Synopsis

Title of Study:
Efficacy and Safety of Tirzepatide Once Weekly in Chinese Participants without Type 2 Diabetes Who Have Obesity or are Overweight with Weight-Related Comorbidities: A Randomized, Double Blind, Placebo Controlled Trial (SURMOUNT-CN)

Rationale:
Obesity is a chronic disease and its increasing prevalence is a public health concern associated with rising incidence of type 2 diabetes mellitus (T2DM), increased risk for premature death and increased risk for some cancers (Allison et al. 2008; AMA 2013; Council on Science and Public Health 2013). Global Health Observatory (GHO) data showed, the number of Chinese people with obesity was below 0.1 million in 1975, rising to 43.2 million in 2014 and accounting for 16.3% of global obesity（World Health Organization [WHO] 2014）. "Report on nutrition and chronic diseases of Chinese Residents（2015）" showed, rate of overweight (body mass index [BMI] ≥24 kg/m^2) in adults age ≥18 years is 30.1%, and rate of obesity (BMI ≥28 kg/m^2) is 11.9%, increasing 7.3% and 4.8% compared to that in 2002, respectively. Although loss of 5% to 10% body weight has been shown to reduce complications related to obesity and improve quality of life (Mertens and Van Gaal 2000; Knowler et al. 2002; Jensen et al. 2014; Li et al. 2014; Warkentin et al. 2014), lifestyle therapies fail to achieve sustainable weight loss in the majority of patients with obesity (Dombrowski et al. 2014).

The gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after meal ingestion and mediate the incretin effect. Both hormones have effects on endocrine cells in the pancreas, increasing insulin biosynthesis and secretion, and modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor (GLP-1R) agonists have been approved for pharmacological treatment of T2DM (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous system), thereby regulating food intake and body weight (Baggio and Drucker 2007). The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the GLP-1R agonist liraglutide for the treatment of overweight and obesity (SAXENDA® package insert, 2014; SAXENDA® SmPc, 2015).

Preclinical data indicate that GIP also exerts effects on appetite regulation and food intake, adipose tissue, and peripheral energy metabolism. Although studies evaluating effects of GIP on body weight have yielded equivocal results, GIP receptor (GIPR) activation may play a role in body weight regulation, and targeting both the GLP-1R and the GIPR simultaneously may result in additive or synergistic effects of the 2 incretins on body weight (Coskun et al. 2018).

Tirzepatide is a 39-amino acid synthetic peptide dual GIP and GLP-1 receptor agonist. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety (Coskun et al. 2018). It is administered once weekly (QW) by subcutaneous (SC) injection.

As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R analogs by recruiting metabolically active tissues not targeted by selective GLP-1R analogs (for example, adipose tissue as indicated by the observation of increased energy utilization) (Baggio and Drucker 2007) and has the potential to reach higher efficacy in target tissues, such as insulin-producing pancreatic beta-cells that express both GIPR and GLP-1R, before reaching its therapeutic limitation. Pre-clinical studies in obese rodents demonstrate that tirzepatide-administered animals lose more weight than animals treated with a selective GLP-1R agonist (GLP-1 RA). This result appears to be due to both enhanced suppression of calorie intake and an increase in energy expenditure (Coskun et al. 2018).

Phase 2 studies I8F-MC-GPGB and I8F-MC-GPGF provided initial safety, tolerability and efficacy data in the tirzepatide 1-to-15-mg dose range when used in treatment of patients with T2DM. In the dose range of 5 to 15 mg, tirzepatide provided significantly greater reductions in hemoglobin A1c (HbA1c) and body weight compared with dulaglutide 1.5 mg QW. Similar to the GLP-1R agonist class, most tirzepatide adverse events (AEs) were dose dependent and gastrointestinal (GI)-related, consisting mainly of nausea, vomiting, and diarrhea. The majority of these events were transient and mild or moderate in severity. Taking the pre-clinical and Phase 2 data together, combined GIP and GLP-1R stimulation with tirzepatide offers a potential new therapeutic option for chronic weight management (Coskun et al. 2018).

Objective(s)/Endpoints:

Objectives	Endpoints
Primary **at 52 weeks, by dose analysis**	
To demonstrate that tirzepatide 10 mg QW is superior to placebo at 52 weeks for • Percent change in body weight AND • Proportion of participants with ≥5% body weight reduction AND/OR To demonstrate that tirzepatide 15 mg QW is superior to placebo at 52 weeks for • Percent change in body weight AND • Proportion of participants with ≥5% body weight reduction	• Mean percent change in body weight from randomization • Percentage of study participants who achieve ≥5% body weight reduction from randomization
Key Secondary (controlled for Type I error) **at 20 weeks, by dose analysis**	
To demonstrate that tirzepatide 10 mg and/or 15 mg QW are superior to placebo at 20 weeks for • Body weight	• Mean change in body weight (kg) from randomization

Key Secondary (controlled for Type I error) at 52 weeks, by dose analysis	
For tirzepatide 10 mg and/or 15 mg QW doses, to demonstrate superiority to placebo in change from randomization for the following (measured at 52 weeks, unless otherwise indicated):	
• Body weight	• Percentage of participants who achieve o ≥10% body weight reduction from randomization o ≥15% body weight reduction from randomization
• Waist circumference	• Mean change in waist circumference (cm) from randomization
Additional Secondary at 52 weeks, by dose analysis	
For tirzepatide 10 mg and/or 15 mg QW doses, to demonstrate superiority to placebo in change from baseline at 52 weeks for the following:	
• Body weight	• Mean change in absolute body weight (kg) from randomization • Mean change in BMI (kg/m^2) from randomization
• Glycemic control	• Mean change in HbA1c (%) from randomization • Mean change in fasting glucose (mmol/L) from randomization
• Patient reported outcomes (SF-36v2 acute form physical functioning)	• Mean change in SF-36v2 acute form physical functioning domain score from randomization
• Patient reported outcomes (IWQOL-Lite-CT physical function composite)	• Mean change in IWQOL-Lite-CT physical function composite score from randomization
Additional Secondary at 52 weeks, pooled analysis	
For tirzepatide (10 and 15 mg combined) QW doses, to demonstrate superiority to placebo in change from baseline at 52 weeks for the following:	
• DBP	• Mean change in DBP (mmHg) from randomization
• SBP	• Mean change in SBP (mmHg) from randomization

• Lipid parameters	• Mean change in fasting lipids (mmol/L) from randomization (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, free fatty acids)
• Insulin	• Mean change in fasting insulin from randomization

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical Trials; LDL = low-density lipoprotein; QW = once weekly; SBP = systolic blood pressure; SF-36v2 acute form = Short-Form 36 Health Survey, version 2, acute form; VLDL = very low-density lipoprotein.

Summary of Study Design:

Study I8F-MC-GPIA(GPIA) is a Phase 3, multicenter, randomized, placebo-controlled, double-blinded study of the safety and efficacy of 10 mg and 15 mg tirzepatide QW, compared with placebo for weight management when used in conjunction with a reduced-calorie diet and increased physical activity, in Chinese participants who do not have T2DM, and have obesity (BMI ≥28 kg/m^2) or are overweight (BMI ≥24 kg/m^2) with at least one weight related comorbidity. Participants will be randomized to 52 weeks treatment to study the effects of tirzepatide on body weight reduction.

Treatment Arms and Duration:

Study participants will be randomized in a 1:1:1 ratio (tirzepatide 10 mg QW, tirzepatide 15 mg QW, and placebo QW), stratified by sex and presence of comorbidities (Y/N).

All participants will undergo a 2-week screening period and a 52-week dose escalation and treatment period, followed by a 4-week safety follow-up period.

Number of Subjects:

Approximately 210 participants will be randomized in a 1:1:1 ratio to 10 mg tirzepatide (70 participants), 15 mg tirzepatide (70 participants), and placebo (70 participants). An upper limit of 70% enrollment of women will be used to ensure a sufficiently large sample of men.

Statistical Analysis:

Efficacy Analysis:

The primary analysis model will be a mixed model for repeated measures (MMRM) for body weight percent change over time and longitudinal logistic regression for proportion of participants achieving at least 5% body weight reduction over time. The response variable of MMRM will be the percent change in body weight from baseline values obtained at each scheduled post baseline visit. The response variable of longitudinal logistic regression will be the proportion of participants achieving at least 5% body weight reduction at each scheduled post baseline visit. The independent variables of both analysis models are treatment group

(tirzepatide 10 mg, tirzepatide 15 mg, and placebo), visit, and treatment-by-visit interaction, stratification factors, and baseline body weight as a covariate. An unstructured covariance structure will model relationship of within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Since the mean percent change in body weight and proportion of participants with ≥5% body weight reduction need to be achieved at the same time, no multiplicity adjustment is planned for these 2 tests.

The primary efficacy analysis will be conducted using the data excluding data after discontinuation of study drug (Efficacy Analysis Set).

Safety Analysis:

Unless specified otherwise, safety assessments will compare safety of tirzepatide doses with placebo irrespective of adherence to study drug. Thus, safety analysis will be conducted using Safety Analysis Set.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all participants enrolled in Study GPIA. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 10 for additional guidance.

Table GPIA.1. Schedule of Activities

Visit[a]	1	2[b]	3	4	5	6	7	8	9	10	11	12	13	14	15	99[c]	ED[d]	801[e]
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**		**4 wks Post TxP**
Allowable Deviation (days)[f]		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**		**±7**
Fasting (>8 hours) Visit[a]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		**X**		**X**	**X**	**X**	**X**
Telephone Visit									**X**	**X**		**X**		**X**				
Informed consent	X																	
Randomization		X																
Register study visit in IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessment																		
Medical history[g]	X																	
Physical examination	X																	
Height	X																	
Weight[h]	X	X	X	X	X	X	X	X			X		X		X	X	X	X
Waist circumference		X	X	X	X	X	X	X			X		X		X	X	X	X
Electrocardiogram[i]		X		X		X					X				X		X	X
Vital signs (3 sitting BP and HR)[j]	X	X	X	X	X	X	X	X			X		X		X		X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Education and Assessment																		
Hand out diary, instruct in use[k]		X	X	X	X	X	X	X			X		X					
Lifestyle Program instructions[l]		X	X	X	X			X			X		X		X		X	
Review diet and exercise goals[k,m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Injection training with Autoinjector demonstration device[k]		X																

Visit[a]	1	2[b]	3	4	5	6	7	8	9	10	11	12	13	14	15	99[c]	ED[d]	801[e]
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**		**4 wks Post TxP**
Allowable Deviation (days)[f]		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**		**±7**
Fasting (>8 hours) Visit[a]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		**X**		**X**	**X**	**X**	**X**
Telephone Visit									**X**	**X**		**X**		**X**				
Dispense study drug		X	X	X	X	X	X	X			X		X					
Observe participant administer study drug[n]		X																
Participant returns study drugs and injection supplies			X	X	X	X	X	X			X		X		X		X	
Review study participant diary, including study drug compliance			X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Laboratory Tests																		
Serum pregnancy test[o]	X																	
Urine pregnancy test[p]		X			X			X			X		X		X	X	X	
Follicle-stimulating hormone[q]	X																	
Chemistry panel (include Cr for eGFR calculation[s] and glucose)	X	X			X			X			X		X		X		X	X
Lipid panel	X	X						X							X		X	X
Insulin		X			X			X			X		X		X		X	X
C-peptide		X			X			X			X		X		X		X	X
Free fatty acids	X	X						X							X		X	X
Urinary albumin/creatinine ratio	X[r]							X							X		X	X
Cystatin-c	X[r]							X							X		X	X

Visit[a]	1	2[b]	3	4	5	6	7	8	9	10	11	12	13	14	15	99[c]	ED[d]	801[e]
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**		**4 wks Post TxP**
Allowable Deviation (days)[f]		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**		**±7**
Fasting (>8 hours) Visit[a]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		**X**		**X**	**X**	**X**	**X**
Telephone Visit									**X**	**X**		**X**		**X**				
Calcitonin	X[r]				X			X							X		X	X
Hematology	X[r]				X			X							X		X	X
HbA1c	X	X			X			X			X		X		X		X	X
Pancreatic amylase, lipase	X	X			X			X							X		X	X
Thyroid stimulating hormone	X[r]																	
Immunogenicity (includes PK sample)[t, u]		X	X		X			X			X				X		X	X
Mental Health Questionnaires																		
Patient Heath Questionnaire-9 (PHQ-9)[v]	X	X			X			X			X		X		X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) (Baseline/Screening Version)[v]	X																	
Columbia-Suicide Severity Rating Scale (C-SSRS) (Since Last Visit Version)[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Supplement Form[v,w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROs[x]																		
Short-Form-36 Health Survey (SF-36), version 2, acute form		X													X		X	

Visit[a]	1	2[b]	3	4	5	6	7	8	9	10	11	12	13	14	15	99[c]	ED[d]	801[e]
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**		**4 wks Post TxP**
Allowable Deviation (days)[f]		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**		**±7**
Fasting (>8 hours) Visit[a]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		**X**		**X**	**X**	**X**	**X**
Telephone Visit									**X**	**X**		**X**		**X**				
Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQOL-Lite-CT)		X													X		X	
EQ-5D-5L		X													X		X	
Patient Global Impression of Status (PGIS) for Physical Activity		X													X		X	

Abbreviations: ADA = antidrug antibodies; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; Cr = creatinine; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HR = heart rate; IWQoL-CT = Impact of Weight on Quality of Life-Lite for Clinical trials; IWRS = interactive web-response system; PGIS = Patient Global Impression of Status; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetics; PRO = patient-reported outcome; SF-36 = Short-Form 36 Health Survey, version 2, acute form; TxP = treatment period; wks = weeks.

[a] For all office visits, study participants should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking study drug(s). Since some screening procedures need to be completed in the fasting state, Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met.

[b] Baseline assessments must be completed before processing in the IWRS.

[c] Participants wanting to discontinue the study before Week 52 will be asked to return for Visit 99 at 52 weeks after randomization for the purpose of body weight and waist circumstance measurement, assessment of adverse events, concomitant medications, urine pregnancy test, and mental health questionnaire. If the participant is unwilling to attend Visit 99, it should be documented in the participant medical record that the participant has refused to attend.

[d] Participants who are unable or unwilling to continue the study treatment for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit.

[e] For participants who discontinue or complete the study within 52 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last visit during the 52-week treatment period.

[f] The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).

[g] Medical history includes assessment of preexisting conditions (including history of gall bladder disease, cardiovascular disease, and medullary thyroid carcinoma) and substance usage (such as alcohol and tobacco).

[h] Weight measurements should be obtained per the instructions in Appendix 8. Body weight must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

[i] ECG should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples.

[j] Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instructions in Appendix 8.

[k] All training should be repeated as needed to ensure participant compliance.

[l] Counselling on diet and exercise, to be performed by a dietician or equivalent qualified delegate, to include calculation of individualized energy requirement and methods to change dietary composition and amount of physical activity. The Lifestyle Program Instruction may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window. Beginning at Week 8, the Lifestyle Program Instruction may be delivered by phone.

[m] Study personnel to provide reinforcement and encouragement for lifestyle modifications.

[n] Participants should administer their first dose of study drug on site at the end of the Visit 2, after other study procedures are completed.

[o] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.

[p] A urine pregnancy test must be performed for all female participants at Visit 2. The result should be available prior to the first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests (beyond those required per the Schedule of Activities) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. For sites who can't perform urine pregnancy test, a local serum pregnancy test can be performed instead.

[q] Follicle-stimulating hormone test performed at Visit 1 for postmenopausal women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for at least 12 months without an alternative medical cause.

[r] Screening visit assessment will be used to confirm eligibility. If calcitonin results are not available, a final review of eligibility will occur at Visit 2 before randomization can proceed.

[s] The CKD-EPI equation will be used by the central lab to estimate and report eGFR.

[t] In the event of systemic drug hypersensitivity reactions (immediate or non-immediate), additional unscheduled blood and urine samples will be collected as detailed in Appendix 6.

[u] PK and ADA samples for immunogenicity must be taken prior to drug administration.

[v] The C-SSRS, Self-Harm Supplement Form and PHQ-9 should be administered *after* assessment of adverse events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed. The C-SSRS questionnaire will be completed by investigators, while PHQ-9 will be completed by participants. The Self-Harm Supplement Form is only required if responses to the C-SSRS indicate that the patient needs to be further evaluated for self-harm risk.

[w] Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form, per instructions in the form. Self-Harm forms will be completed by investigators.

[x] All PROs should be completed before any other study procedures if the participant is not adversely affected by the fasting condition or completed after the participant has sufficiently recovered from the preceding visit procedures.

3. Introduction

Obesity is a chronic disease and its increasing prevalence is a public health concern associated with rising incidence of type 2 diabetes mellitus (T2DM), increased risk for premature death and increased risk for some cancers (Allison et al. 2008; AMA 2013; Council on Science and Public Health 2013). Although loss of 5% to 10% body weight has been shown to reduce complications related to obesity and improve quality of life (Mertens and Van Gaal 2000; Knowler et al. 2002; Jensen et al. 2014; Li et al. 2014; Warkentin et al. 2014), lifestyle therapies fail to achieve sustainable weight loss in the majority of patients with obesity (Dombrowski et al. 2014).

3.1. Study Rationale

The gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted after meal ingestion and mediate the incretin effect. Both hormones have effects on endocrine cells in pancreas, increasing insulin biosynthesis and secretion, stimulating beta-cell neogenesis and proliferation, and protecting beta cells from apoptosis. They also exert actions on alpha cells, modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor (GLP-1R) agonists have been approved for pharmacological treatment of T2DM (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1R activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1R activation in the central and peripheral nervous system), thereby regulating food intake and body weight (Baggio and Drucker 2007). The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the GLP-1R agonist liraglutide for the treatment of overweight and obesity (SAXENDA® package insert, 2014; SAXENDA® SmPc, 2015).

Preclinical data indicate that GIP exerts effects on appetite regulation and food intake, on adipose tissue and on peripheral energy metabolism. Although studies evaluating effects of GIP on body weight have yielded equivocal results, GIP receptor (GIPR) activation may play a role in body weight regulation, and targeting both the GLP-1R and the GIPR simultaneously may result in additive or synergistic effects of the 2 incretins on body weight (Coskun et al. 2018).

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIPR and GLP-1R. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety (Coskun et al. 2018). It is administered once weekly (QW) by subcutaneous (SC) injection.

As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R analogs by recruiting metabolically active tissues not targeted by selective GLP-1R analogs (for example, adipose tissue as indicated by the observation of increased energy utilization) (Baggio and Drucker 2007) and has the potential to reach higher efficacy in target tissues, such as insulin-producing pancreatic beta-cells that express both GIPR and GLP-1R, before reaching its therapeutic limitation.

In a 26-week Phase 2 study (I8F-MC-GPGB) of participants with T2DM, tirzepatide reduced body weight by 4.8 kg, 8.7 kg, and 11.3 kg at dose levels of 5, 10, and 15 mg, respectively,

whereas the weight loss observed in participants on dulaglutide, a selective GLP-1R agonist, used at the dose of 1.5 mg, was 2.7 kg (Frias et al. 2018). Similar to the GLP-1R agonist class, most of the tirzepatide adverse events (AEs) were dose dependent and gastrointestinal (GI)-related, consisting mainly of nausea, vomiting, and diarrhea. The majority of these events were transient and mild or moderate in severity.

Taking the preclinical and Phase 2 data together, combined GIP and GLP-1R stimulation with tirzepatide offers a potential new therapeutic option for chronic weight management (Coskun et al. 2018).

Study I8F-MC-GPIA(GPIA) is a Phase 3, multicenter, randomized, placebo-controlled, double-blinded study of the safety and efficacy of 10 mg and 15 mg tirzepatide QW, compared with placebo for weight management when used in conjunction with a reduced-calorie diet and increased physical activity, in Chinese participants who do not have T2DM, and have obesity (body mass index [BMI] ≥28 kg/m^2) or are overweight (BMI ≥24 kg/m^2) with at least one weight related comorbidity. Participants will be randomized to 52 weeks treatment to study the effects on body weight reduction.

3.2. Background

Despite the extraordinarily adverse impact of overweight and obesity on patients and the healthcare system, there is a paucity of approved pharmacologic interventions to aid the treatment of obesity. Only orlistat, a drug that blocks absorption of dietary fat, is approved in China as over-the-counter drug (Kim et al. 2014; Pilitsi et al. 2019). Currently, bariatric surgery is considered as the most potent clinical intervention for weight management. However, bariatric surgery has risks, including periprocedural complications. For some individuals who have obesity/overweight, pharmacological management could be a preferred option. In addition, bariatric surgery does not exclude pharmacological intervention before or after the intervention. Thus, there remains an unmet need in the pharmacologic treatment of obesity for drugs that are safe, efficacious and well tolerated. (Livingston et al. 2010)

As a dual agonist, tirzepatide binds both GIP and GLP-1 receptors and combines the signaling of each receptor. Preclinical studies in obese rodents demonstrate that tirzepatide-administered animals lose more weight than animals treated with a selective GLP-1 RA. This result appears to be due to both enhanced suppression of calorie intake and an increase in energy expenditure (Coskun et al. 2018). Tirzepatide has been associated with significant dose-dependent weight loss at both the 10 and 15 mg doses in Phase 2 studies (Frias et al. 2018).

Dose selection for obesity treatment has been informed by 3 clinical trials: a Phase 1 study, Study I8F-MC-GPGA (GPGA), and two Phase 2 studies, Study I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF).

Phase 1 Study GPGA was a combination of single ascending dose (SAD) and multiple ascending dose (MAD) studies in healthy subjects and a multiple dose study in patients with T2DM. A total of 142 participants (89 healthy subjects and 53 patients with T2DM) received at least 1 dose of treatment. Doses of tirzepatide ranged from:

- 0.25 mg to 8 mg in the SAD (with maximum tolerated dose achieved at 5 mg)
- multiple doses from 0.5 mg to 4.5 mg QW and titrated doses up to 10 mg QW for 4 weeks in healthy subjects
- multiples doses at 0.5 mg and 5 mg QW and titrated to 15 mg QW for 4 weeks in patients with T2DM in the MAD

The safety and tolerability and pharmacokinetic/pharmacodynamic (PK/PD) profiles of tirzepatide at doses and escalation regimens administered in this Phase 1 study supported further development of tirzepatide for QW dosing in patients with T2DM.

Phase 2 studies I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF) provided initial safety, tolerability and efficacy data for tirzepatide 10 mg and 15 mg when used in treatment of patients with T2DM. Tirzepatide 10 mg and 15 mg provided significantly greater reductions in HbA1c and body weight compared with dulaglutide 1.5 mg QW. The most common AEs, which were also dose dependent, were mild to moderate nausea, vomiting, and diarrhea. Study GPGF showed that adjustments in the tirzepatide dose-escalation algorithm resulted in additional reductions in the frequency of GI AEs and reduced the frequency of treatment discontinuations due to GI AEs.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of tirzepatide are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table GPIA.2. shows the objectives and endpoints of the study.

Table GPIA.2. Objectives and Endpoints

Objectives	Endpoints
Primary at 52 weeks, by dose analysis	
To demonstrate that tirzepatide 10 mg QW is superior to placebo at 52 weeks for • Percent change in body weight AND • Proportion of participants with ≥5% body weight reduction AND/OR To demonstrate that tirzepatide 15 mg QW is superior to placebo at 52 weeks for • Percent change in body weight AND • Proportion of participants with ≥5% body weight reduction	• Mean percent change in body weight from randomization • Percentage of study participants who achieve ≥5% body weight reduction from randomization
Key Secondary (controlled for Type I error) at 20 weeks, by dose analysis	
To demonstrate that tirzepatide 10 mg and/or 15 mg QW are superior to placebo at 20 weeks for • Body weight	• Mean change in body weight (kg) from randomization
Key Secondary (controlled for Type I error) at 52 weeks, by dose analysis	
For tirzepatide 10 mg and/or 15 mg QW doses, to demonstrate superiority to placebo in change from randomization for the following (measured at 52 weeks, unless otherwise indicated): • Body weight • Waist circumference	• Percentage of participants who achieve o ≥10% body weight reduction from randomization o ≥15% body weight reduction from randomization • Mean change in waist circumference (cm) from randomization

Additional Secondary at 52 weeks, by dose analysis	
For tirzepatide 10 mg and/or 15 mg QW doses, to demonstrate superiority to placebo in change from baseline at 52 weeks for the following:	
• Body weight	• Mean change in absolute body weight (kg) from randomization • Mean change in BMI (kg/m^2) from randomization
• Glycemic control	• Mean change in HbA1c (%) from randomization • Mean change in fasting glucose (mmol/L) from randomization
• Patient reported outcomes (SF-36v2 acute form physical functioning)	• Mean change in SF-36v2 acute form physical functioning domain score from randomization
• Patient reported outcomes (IWQOL-Lite-CT physical function composite)	• Mean change in IWQOL-Lite-CT physical function composite score from randomization
Additional Secondary at 52 weeks, pooled analysis	
For tirzepatide (10 and 15 mg combined) QW doses, to demonstrate superiority to placebo in change from baseline at 52 weeks for the following:	
• DBP	• Mean change in DBP (mmHg) from randomization
• SBP	• Mean change in SBP (mmHg) from randomization
• Lipid parameters	• Mean change in fasting lipids (mmol/L) from randomization (total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, triglycerides, free fatty acids)
• Insulin	• Mean change in fasting insulin from randomization
Tertiary/Exploratory	
To assess changes from baseline in patient-reported outcomes:	Mean change from randomization to week 52 regarding the following parameters: • SF-36v2 acute form Mental Component Score (MCS)

• To assess changes from baseline in health-related quality of life as measured by the SF-36v2 acute form • To assess changes from baseline in obesity-related quality of life as measured by the IWQOL-Lite-CT • To assess changes from baseline in health status as measured by the EQ-5D-5L	• SF-36v2 acute form Physical Component Score (PCS) • SF-36v2 acute form Role-Physical domain (RP) • SF-36v2 acute form Bodily Pain domain (BP) • SF-36v2 acute form General Health domain (GH) • SF-36v2 acute form Vitality domain (VT) • SF-36v2 acute form Social Functioning domain (SF) • SF-36v2 acute form Role-Emotional domain (RE) • SF-36v2 acute form Mental Health domain (MH) • IWQOL-Lite-CT total score • IWQOL-Lite-CT Physical composite score • IWQOL-Lite-CT Psychosocial composite score • EQ-5D-5L utility score • EQ-5D-5L VAS score
Pharmacokinetics • To characterize the PK of tirzepatide 10 mg and 15 mg QW and evaluate the relationship between tirzepatide exposure and safety, tolerability, and efficacy measures.	• Population PK and PD parameters

Abbreviations: BMI = body mass index; BP = Bodily Pain domain; GH = General Health domain; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite for Clinical trials; LDL = low-density lipoprotein; MCS = Mental Component Score; MH = Mental Health domain; PCS = Physical Component Score; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; RE = Role-Emotional domain; RP = Role-Physical domain; SBP = systolic blood pressure; SF = Social Functioning domain; SF-36v2 acute form = Short-Form-36 Health Survey, version 2, acute form; VAS = visual analogue scale; VLDL = very low-density lipoprotein; VT = Vitality domain.

5. Study Design

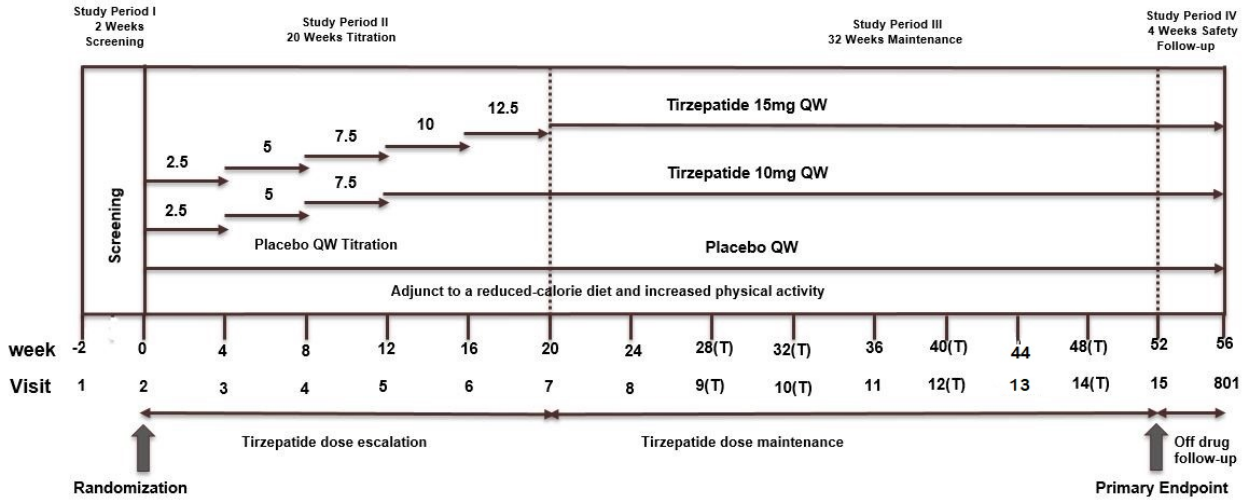
5.1. Overall Design

Study GPIA is a Phase 3, multicenter, randomized, double-blinded, placebo-controlled study that will investigate the effects of treatment with tirzepatide 10 mg and 15 mg QW compared with placebo on weight loss in Chinese participants without T2DM who either have obesity (BMI ≥28 kg/m^2) or overweight (BMI ≥24 kg/m^2) with the presence of at least one weight-related comorbidity. The co-primary endpoints will be mean percent change in body weight and proportion of participants reaching ≥5% total body weight loss, measured from randomization to Week 52.

Study participants will be randomized in a 1:1:1 ratio (tirzepatide 10 mg QW, tirzepatide 15 mg QW, and placebo). An upper limit of 70% enrollment of women will be used to ensure a sufficiently large sample of men.

All participants will undergo a 2-week screening period and a 52-week dose escalation and treatment period, followed by a 4-week safety follow-up period.

Figure GPIA.1. illustrates the study design.



Abbreviations: QW=once weekly; T = telephone visit.

Figure GPIA.1. Illustration of study design for Clinical Protocol I8F-MC-GPIA.

5.1.1. Overview of Study Periods

5.1.1.1. Visit Structure for all Office Visits

On all designated fasting office visits, study participants are required to report to the site in a fasting condition, after approximately 8 hours without eating, drinking (except water), or performing any significant physical activity. If a participant is adversely affected by the fasting condition, they are allowed to eat, however, specific study procedures need to be completed while fasting.

5.1.1.2. Main Study Period

5.1.1.2.1. Screening Period

Visit 1

The purpose of screening procedures at Visit 1 is to establish initial eligibility, and to obtain blood samples for laboratory assessments needed to confirm eligibility. Participants should arrive to the clinic in the fasting state (after approximately 8 hours without eating, drinking [except water], or any significant physical activity). The participant must sign the informed consent form (ICF) before the study procedures are performed, as outlined in the Schedule of Activities, Section 2. Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met. Participants who meet all applicable inclusion criteria and none of the applicable exclusion criteria (Sections 6.1 and 6.2) at Visit 1 will continue to Visit 2.

5.1.1.2.2. Treatment Period

Randomization (Visit 2)

At Visit 2, eligible participants will perform all required baseline study procedures (including the collection of all baseline laboratory measures and questionnaires) prior to randomization and prior to taking the first dose of study drug. Participants should arrive to the clinic in the fasting state (after a period of approximately 8 hours without eating, drinking [except water], or any significant physical activity and before taking study drug(s)). The mental health questionnaires (Patient Heath Questionnaire-9 [PHQ-9], Columbia-Suicide Severity Rating Scale [C-SSRS], and Self-Harm Form) should be completed after the assessment for AEs.

Participants will receive an initial consultation with a qualified dietitian, according to local standards, to set lifestyle goals for caloric intake and physical activity (Sections 6.3.1 and 6.3.2).

Following randomization, study site personnel will demonstrate use of the autoinjector and observe the study participant inject the first dose of tirzepatide or placebo. The date and time of the first dose of study drug will be recorded on the electronic case report form (eCRF). Beginning at randomization, all participants will receive study drug according to the randomized treatment arm for the duration of the 52-week dose escalation and treatment period.

Treatment Period (End of Visit 2 to Visit 15):

During the treatment period, visits will occur every 4 weeks through 52 weeks. The participant should be fasting for all office visits. Weeks 28, 32, 40 and 48 are telephone visits.

Office visit procedures should be conducted according to the Schedule of Activities (Section 2), and will include

- weight, waist circumference, and vital signs measurements
- review of participant diary information (to include reinforcement and compliance assessments for study drug administration and lifestyle goals)
- administration of questionnaires
- laboratory testing
- drug dispensing, and

- collect AEs and concomitant medications.

Patient-Reported Outcomes (PROs) questionnaires should be administered as early as possible, prior to any other study procedures. All PROs should be completed before any other study procedures if the participant is not adversely affected by the fasting condition or completed after the participant has sufficiently recovered from the preceding visit procedures. Mental Health Questionnaires should be completed after the assessment of AEs.

Dietitian consultations start at Week 0 and continue at Weeks 4, 8, 12, 24, 36, 44, 52 and early discontinuation (ED). Study drug and injection supplies will be returned per the Schedule of Activities (Section 2) and according to local requirements. New supplies will be dispensed as needed.

Study drug dose escalation is double-blinded and will be managed via the interactive web-response system (IWRS). The starting dose is 2.5 mg QW (or matching placebo) for 4 weeks, then the dose is increased by 2.5 mg (or matching placebo) every 4 weeks (2.5 to 5 to 7.5 to 10 mg) for those randomized to 10 mg, continuing to 12.5 to 15 mg for those randomized to 15 mg. The dose is then maintained for the remainder of the study.

At each of the 4 scheduled telephone visits, procedures will include:

- reinforcement and compliance assessments for study drug administration and lifestyle goals
- listing of concomitant medications
- AE assessment (see Schedule of Activities Section 2), and
- completion of the mental health questionnaires (after the AE assessment).

Participants should be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties administering their study medication. Participants should also be advised about the appropriate course of action in the event that study drug is not taken at the required time (late/missing doses).

Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications (see Section 6.2) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Visit 99

Visit 99 is only applicable to participants who discontinue the study treatment prematurely before 52 weeks and decline to complete the remaining study visits but are willing to return for Visit 99 at 52 weeks after randomization. This visit is critical to ensure complete data collection for the primary weight loss endpoint.

Participants should attend this visit in the fasting state. Procedures to be completed are:

- measurement of weight and waist circumference
- listing of concomitant medications
- urine pregnancy test

- assessment of AEs, and
- completion of the mental health questionnaires (after the AE assessment)

For participants unwilling to attend this visit, their refusal to attend should be documented in the participant medical record.

5.1.1.2.3. Safety Follow-up Period

Visit 801

All participants are required to complete Visit 801, a safety follow-up visit. Participants discontinuing the study early and performing an early discontinuation (ED) visit will also be asked to perform the safety follow-up visit. During the safety follow-up period, participants will not receive study drug. Participants are also required to return any remaining study diaries to the study site at the end of this period.

For participants who discontinue or complete the study within the first 52 weeks, Visit 801 (safety follow-up visit) should be performed 4 weeks after the last treatment visit (Visit 99 or 15, respectively) or 4 weeks after the ED visit for those who decline to return for Visit 99.

5.1.1.2.4. Early Discontinuation Visit

Participants unable or unwilling to continue the study treatment for any reason will perform an ED visit. Procedures should be completed according to the Schedule of Activities (Section 2). Patient-reported outcomes questionnaires should be completed as early as possible, prior to other study procedures. Administration of Mental Health Questionnaires should follow assessment for AEs (see Section 8.2).

5.2. Number of Participants

Approximately 210 participants will be randomized in a 1:1:1 ratio to 10 mg tirzepatide (70 participants), 15 mg tirzepatide (70 participants), and placebo (70 participants).

5.3. End of Study Definition

Section 8.2 describes the criteria used to determine if a participant has completed the study.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (Section 2).

5.4. Scientific Rationale for Study Design

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIPR and GLP-1R. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety (Coskun et al. 2018). It is administered QW by SC injection.

As a dual GIP/GLP-1R agonist, tirzepatide could exceed the efficacy of selective GLP-1R agonists by recruiting metabolically active tissues not targeted by selective GLP-1R agonists (for example, adipose tissue as indicated by the observation of increased energy utilization) (Baggio and Drucker 2007) and has the potential to reach higher efficacy in target tissues, such as insulin-producing pancreatic beta-cells that express both GIPR and GLP-1R, before reaching its

therapeutic limitation. Results from a Phase 2 study (GPGB) demonstrated that tirzepatide use in participants with T2DM was associated with a substantial, dose-dependent weight loss, greater than the weight change observed with dulaglutide, a specific GLP1R agonist. General safety characteristics of all studied doses of tirzepatide were similar to that of the GLP-1R agonist class, consisting mainly of nausea, vomiting, and diarrhea. In general, these events were transient and mild or moderate in severity, with few severe episodes. Although GI AEs were more common at 15-mg arm of tirzepatide, the dose demonstrated the highest efficacy in terms of weight loss.

This suggests that tirzepatide has the potential to become a medication for chronic weight management. An optimized dose escalation regimen being used in global Phase 3 studies for both diabetes and chronic weight management, and being proposed in the study GPIA to improve tolerability should enable a use of higher doses to maximize effects on body weight.

Study GPIA is designed to determine the comparative benefits and risks of tirzepatide 10 mg or 15 mg QW versus placebo in Chinese participants who have obesity or overweight. A double-blinded design was selected to minimize participant and investigator bias in assessments for efficacy, safety, and study drug tolerability.

A placebo comparator was selected for this trial in accordance with regulatory guidance (FDA 2007; EMA 2016). In addition, all participants, regardless of treatment assignment, will receive lifestyle modification counselling consistent with current guidelines for weight management (Jensen et al. 2013). Specifically, participants will consult with a dietitian, or equivalent qualified delegate, throughout the study to achieve at least a 500 kcal/day energy deficit through a combination of caloric restriction and increased physical activity (see Section 6.3).

The planned duration of treatment for the primary endpoint at 52 weeks allows for a 40-week treatment period at the dose achieved 10 mg and 32-week treatment period at the dose achieved 15 mg following dose escalation. This duration is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of tirzepatide compared with placebo on body weight.

The effects of drug cessation will be assessed in the 4-week safety follow-up/observational period.

To minimize the potential confounding effect of changes to concomitant medications, participants will be permitted to use concomitant medications that do not interfere with the assessment of efficacy or safety characteristics of the study treatments.

5.5. Justification for Dose

Tirzepatide doses of 10 mg, and 15 mg QW will be evaluated in this study. These doses and associated escalation schemes were selected based on assessment of safety, efficacy (weight loss), and GI tolerability data, followed by exposure-response modeling of data in patients in Phase 1 and 2 studies.

In a 26-week Phase 2 study (GPGB) of participants with T2DM, tirzepatide reduced body weight by 8.7 kg, and 11.3 kg at dose levels of 10, and 15 mg, respectively, whereas the weight loss

observed in participants on dulaglutide, a selective GLP-1R agonist, used at the dose of 1.5 mg, was 2.7 kg (Frias et al. 2018).

Similar to the GLP-1R agonist class, most of the tirzepatide AEs were dose dependent and GI-related, consisting mainly of nausea, vomiting, and diarrhea. In general, these events were mild or moderate in severity, with few severe episodes, and transient.

Tirzepatide doses of 10 mg, and 15 mg were selected based principally on the following criteria

- each dose provides robust weight loss relative to placebo
- the percent of patients achieving >10% weight loss is higher with 15 mg than 10 mg, and
- safety and tolerability were supported by Phase 2 results and/or PK/PD modeling.

A subsequent Phase 2 study (GPGF) evaluating different titration schemes demonstrated that slower dose escalation and smaller dose increments might improve tolerability. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks should permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns. The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no-observed adverse effect level doses in 6-month monkey and rat toxicology studies.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Have a BMI
   - ≥28 kg/m^2 or
   - ≥24 kg/m^2 and previously diagnosed with at least one of the following weight related comorbidities:
     - Hypertension: treated or with systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg
     - Dyslipidemia: treated or with low-density lipoprotein (LDL) ≥4.1 mmol/L (160 mg/dL) or triglycerides ≥1.7 mmol/L (150 mg/dL), or high-density lipoprotein (HDL) <1.0 mmol/L (40 mg/dL) for men or HDL<1.3 mmol/L (50 mg/dL) for women
     - Obstructive sleep apnea
     - Cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association [NYHA] Functional Class I-III heart failure)
2. Have a history of at least one self-reported unsuccessful dietary effort to lose body weight
3. In the investigator's opinion, are well-motivated, capable, and willing to
   - learn how to self-inject study drug, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)
   - inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations)
   - follow study procedures for the duration of the study, including, but not limited to: follow lifestyle advice (for example, dietary restrictions and exercise plan), maintain a study diary, and complete required questionnaires

Participant Characteristics

4. Are 18 years or older
   a. Male participants:

- Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods throughout the study and for 4 months after the last injection.

b. Female participants:

- Female participants not of childbearing potential may participate and include those who are:
  - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy or tubal ligation), congenital anomaly such as Mullerian agenesis
  - postmenopausal, defined as either
    - a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone ≥40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry

    or

    - a woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea

    or

    - a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy
- Female participants of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:
    - test negative for pregnancy at Visit 1 based on a serum pregnancy test

  AND

    - if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective, for the duration of the trial and for 30 days thereafter (Appendix 7)
    - not be breastfeeding

Informed Consent

5. Have given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing the study site

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

Diabetes-related

6. Have type 1 diabetes mellitus (T1DM) or T2DM, history of ketoacidosis, or hyperosmolar state/coma
7. Have HbA1c ≥6.5% or fasting serum glucose (FSG) ≥7.0 mmol/L, as determined by the central laboratory at Visit 1

Obesity-related

8. Have a self-reported change in body weight >5 kg within 3 months prior to screening
9. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty if performed >1 year prior to screening)
10. Have or plan to have endoscopic and/or device-based therapy for obesity or have had removal within the last 6 months (for example, mucosal ablation, gastric artery embolization, intragastric balloon and duodenal-jejunal endoluminal barrier)

Other medical

11. Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology as determined by central laboratory during screening
12. Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility
13. Have had a history of chronic or acute pancreatitis
14. Have a thyroid stimulating hormone (TSH) <0.4 or >6.0 mIU/L at screening visit

    ***Note**:* Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 3 months.

    Note: TSH values above the normal range can, in some participants, suggest subclinical hypothyroidism. If, in the investigator's opinion, the participant has subclinical hypothyroidism and may require initiation of thyroid hormone replacement during the course of the study, the participant should be excluded from the study.
15. Have obesity induced by other endocrinologic disorders (for example, Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome)
16. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years

Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications

17. Have any lifetime history of a suicidal attempt
18. Have a PHQ-9 score of 15 or more at Visit 1 or 2, prior to randomization.
19. On the C-SSRS at Visits 1 or 2, prior to randomization:
    - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C−SSRS, or
    - answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

    and
    - the ideation or behavior occurred within the past month
20. Have uncontrolled hypertension (systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg)
21. Have any of the following cardiovascular conditions within 3 months prior to randomization: acute myocardial infarction, cerebrovascular accident (stroke), unstable angina, or hospitalization due to congestive heart failure (CHF)
22. Have NYHA Functional Classification IV CHF
23. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory during screening:
    - Alanine aminotransferase (ALT) level >3.0x the upper limit of normal (ULN) for the reference range

    or
    - Alkaline phosphatase (ALP) level >1.5x the ULN for the reference range

    or
    - Total bilirubin (TBL) level >1.2x the ULN for the reference range (except for cases of known Gilbert's Syndrome)

***Note**:* Participants with nonalcoholic fatty liver disease (NAFLD) <u>are eligible</u> to participate in this trial if their ALT level is ≤3.0x ULN for the reference range.

24. Have a calcitonin level (at Visit 1) of:
    - ≥20 ng/L at Visit 1, if eGFR ≥60 mL/min/1.73 m^2
    - ≥35 ng/L at Visit 1, if eGFR <60 mL/min/1.73 m^2

25. Have a family or personal history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia (MEN) syndrome type 2
26. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years
27. Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1R agonists
28. Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol
29. Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
30. Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease)

Prior/Concomitant Therapy

31. Are receiving or have received within 3 months prior to screening chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intra-ocular, intranasal, intra-articular or inhaled preparations) in the next 12 months
32. Have current or history of (within 3 months prior to randomization) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotic and mood stabilizers for example:
    - imipramine
    - amitriptyline
    - mirtazapine
    - paroxetine
    - phenelzine
    - chlorpromazine
    - thioridazine
    - clozapine
    - olanzapine
    - valproic acid and its derivatives, and
    - lithium

    Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted.

33. Have taken within 3 months prior to randomization, medications (prescribed or over-the-counter) or alternative remedies intended to promote weight loss. Examples include, but are not limited to
    - Xenical® (orlistat)

    Note: Use of metformin or any other glucose-lowering medication, whether prescribed for polycystic ovary syndrome or diabetes prevention is not permitted.

34. Have started implantable or injectable contraceptives (such as Depo-Provera®) within 18 months prior to screening

Prior/Concurrent Clinical Study Experience

35. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

36. Within the last 30 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an investigational product, 5 half-lives or 30 days, whichever is longer, should have passed

Other Exclusions

37. Are investigator site personnel directly affiliated with this study and/or their immediate family (immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted)

38. Are Eli Lilly and Company (Lilly) employees

6.3. Lifestyle Restrictions

Per the Schedule of Activities (Section 2), participants will consult with a dietician, or equivalent qualified delegate, according to local standards, to receive lifestyle management counseling at Weeks 0, 4, 8 and 12 during dose escalation and then at Week 24, 36, 44, 52 and ED.(Section 2).

Diet and exercise goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the trial will be reinforced at each trial contact by study staff.

6.3.1. Meals and Dietary Restrictions

At Visit 2 and subsequent visits study participants will receive diet counselling by a dietician/nutritionist, or equivalent qualified delegate, according to local standard. Dietary counseling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of:

- approximately 20%-30% of energy from fat
- approximately 15%-20% of energy from protein
- approximately 40-55% of energy from carbohydrates, and

- with an energy deficit of approximately 500 kcal/day compared to the participant's total daily energy or use the equation: (body height (cm) - 105) × 25 kcal/day as calorie restrict diet energy target (Committee of China expert consensus of medical nutrition therapy to patients who are overweight or obese, 2016; Ge et al. 2018)

To encourage adherence, it is recommended that a 3-day food and exercise diary be completed prior to each counseling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed.

The hypocaloric diet is continued after randomization and throughout the treatment period. If a BMI ≤20 kg/m^2 is reached the recommended energy intake should be recalculated with no kcal deficit for the remainder of the trial. Also, it is recommended total daily energy is at least 1000 kcal for women and at least 1200 kcal for men.

6.3.2. Physical Activity

At Visit 2 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomly assigned to the study intervention. A minimal set of screen failure information should be collected to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) should not be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of 10 mg and 15 mg tirzepatide administered by subcutaneous injection once weekly with placebo. Table GPIA.3 shows the treatment regimens.

Table GPIA.3. Treatment Regimens

ARM Name	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Dose[a]	10 mg QW	15 mg QW	N/A
Route of Administration	SC	SC	SC
Sourcing	Provided centrally by the Sponsor and dispensed via IWRS		

Abbreviations: IWRS = interactive web response service; N/A= not available, QW= once-weekly, SC= subcutaneous

[a] Tirzepatide treatment will follow a fixed dose escalation that initiated at 2.5 mg QW for 4 weeks and increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the desired dose is achieved and maintained for the duration of the study.

7.1.1. Packaging and Labelling

Study Intervention will be provided in investigational autoinjectors, packaged in cartons to be dispensed. Clinical study materials will be labeled according to China regulatory requirements.

7.1.2. Medical Devices

The investigational combination products provided for use in the study are tirzepatide investigational autoinjectors (or matching placebo). Any medical device related adverse event, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 9.2.3).

7.2. Method of Treatment Assignment

Participants who meet all criteria for enrollment will be randomized to one of the study treatment groups at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. Participants will be randomized in a 1:1:1 ratio to receive tirzepatide 10 mg, tirzepatide 15 mg, or placebo.

The randomization will be stratified by sex (female, male) and presence of comorbidities (Y/N).

7.2.1. Selection and Timing of Doses

There are no restrictions on the time of day each weekly dose of study drug is given, but it is advisable to administer the SC injections on the same day and same time each week. The actual date and time of all dose administrations will be recorded by the participant. If a dose of study drug is missed, the participant should take it as soon as possible unless it is within 72 hours of

the next dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time. The day of weekly administration can be changed if necessary, as long as the last dose was administered 72 or more hours before.

All participants will inject study drug subcutaneously in the abdomen or thigh by following the Instructions for Use provided for the study, and using the injection supplies provided; a caregiver may administer the injection in the participant's upper arm. A new autoinjector will be used for each injection. If study drug is to always be injected in the same body region, participants should be advised to rotate injection sites.

7.3. Blinding

This is a double-blind study.

Investigators, site staff, clinical monitors and participants will remain blinded to the treatment assignments until the study is completed.

Emergency unblinding may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All emergency unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study drug. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible

7.4. Dosage Modification

7.4.1. Tirzepatide

Study drug dose modification is not permitted, except for management of intolerable GI symptoms (see Section 7.4.2).

7.4.2. Management of Participants with Gastrointestinal Symptoms

Participants who experience intolerable GI symptoms (for example: nausea, vomiting, or diarrhea) at any time during the study, should first be counselled on dietary behaviors that may help mitigate nausea and vomiting, (for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full). If symptoms persist, the participant should be prescribed, at the investigator's discretion, symptomatic medication (for example, antiemetic or antidiarrheal medication). A temporary interruption of study drug for 1

dose is permitted, provided the participant has taken the last 3 weekly doses. Study treatment should be resumed at the assigned dose immediately, either alone or in combination with symptomatic medication (Appendix 9). Management of study drug after interruptions >1 dose is discussed in Section 8.1.2.

If intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures, the investigator should contact Lilly to consider reinitiating study drug at the next lowest maintenance dose in a blinded fashion (for example, 15 mg and 12.5 mg reduced to 10 mg, 10 mg or lower reduced to placebo, the lower dose will be maintained for the rest of the study, with no re-escalation allowed).

If intolerable GI symptoms persist despite symptomatic treatment, temporary drug interruption, and resumption at a lower dose of study drug, the participant should be discontinued from the study drug. Only 1 dose reduction per participant will be permitted during the course of the study. All participants who discontinue study drug should continue to attend scheduled study visits. All dose adjustments will be managed through IWRS.

7.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention (includes study drug and autoinjectors) accountability, reconciliation, and record maintenance (for example, receipt, reconciliation, and final disposition records).
- Study site staff must regularly assess whether the participant is correctly administering the assigned study drug and storing the study drug according to the provided instructions.

7.6. Treatment Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting of unused study drug and/or empty cartons returned. Study drug compliance will be determined by the following:

- Study drug administration data will be recorded by the participant and reviewed by the investigator at each study visit.
- The participants will be instructed to return any unused study drug and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

Treatment compliance for each visit interval is defined as taking at least 75% of the required doses of study drug. Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication (more than 125%).

In addition to the assessment of a participant's compliance with study drug administration, other aspects of compliance with the study treatments will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study diaries, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

7.7. Concomitant Therapy

Participants will be permitted to use concomitant medications that they require during the study, except certain medications (for example, other medications for weight management) that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Participants who develop diabetes during the study may initiate medication for glucose control per local standard of care, with the exception of dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1R agonists. Initiation of metformin for the treatment of diabetes is permitted, but metformin should not be initiated during the study for the treatment of other metabolic conditions (for example, polycystic ovary syndrome, diabetes prevention).

Investigative site staff will inform participants that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case, the participant will inform the investigator or a designated site staff member as soon as possible.

Nonstudy medications taken by participants who are screened but not randomized will not be reported to Lilly unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

7.8. Treatment after the End of the Study

Tirzepatide will not be made available after conclusion of the study to participants.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Participant Decision**
  - The participant requests to discontinue investigational product.
- **Clinical considerations**
  - Initiation of open-label GLP-1R agonist or DPP-4 inhibitor, if participants will not or cannot discontinue them
  - Intolerable GI symptoms despite management as described in Section 7.4.2.
  - BMI ≤18.5kg/m^2 is reached at any time during the treatment period

    Note: The investigator should contact the Sponsor CRP to discuss whether it is medically appropriate for the participant to continue study treatment
  - Diagnosis of T1DM
  - Diagnosis of MTC after randomization
  - Significant elevation of serum calcitonin (Appendix 6)
  - Diagnosis of acute or chronic pancreatitis
  - Diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
  - If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the investigational drug
  - Onset of pregnancy in a female participant
  - Occurrence of any other treatment-emergent AE (TEAE), SAE, or clinically significant finding for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
  - Inadvertent enrollment if continued treatment with study drug would not be medically appropriate (Section 8.1.3)
  - PHQ-9 score ≥15
    - Participants should be referred to a Mental Health Professional (MHP) to assist in deciding whether the participant should be discontinued from study drug. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the participant, at the discretion of the Investigator (in agreement with the MHP), may be continued in the trial on randomized therapy.
  - In addition, study drug may be discontinued if participants
    - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**

- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

- **Discontinuation due to a hepatic event or liver test abnormality.**
  - Participants who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.
  - Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a participant meets one of the following conditions after consultation with the Lilly designated medical monitor:
    - ALT or AST >8x ULN
    - ALT>2x baseline value OR ≥300U/L, whichever occurs first, if

      baseline ALT≥2x ULN
    - ALT or AST >5x ULN for more than 2 weeks
    - ALT or AST >3x ULN and TBL >2x ULN or international normalized ratio (INR) >1.5
    - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - ALP >3x ULN
    - ALP >2.5x ULN and TBL >2x ULN
    - ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Participants who stop the study drug permanently should continue to attend all scheduled study visits to collect all planned efficacy and safety measurements. Participants who are unwilling to attend all scheduled visits and stop the study prior to 52 weeks, should return for a final weight measurement (Visit 99). If participants are unwilling to attend visit 99, their refusal to attend should be documented in the patient medical record.

Participants discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

In certain situations after randomization, the investigator may need to temporarily interrupt study drug. Every effort should be made by the investigator to maintain participants on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so. Distribution of study medication at the correct dose will be per IWRS instructions.

- If the study drug interruption is ≤2 consecutive doses, the drug will be restarted at last administered dose, as per the escalation schedule.
- If the interruption is >2 consecutive doses, the participant will restart study drug at 5 mg (per IWRS instructions) and repeats dose escalation scheme.
- If study drug interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol.
- If the study drug interruption is due to intolerable persistent GI AE (for example, nausea, vomiting, or diarrhea), the participants should be treated as suggested in Section 7.4.2.

Investigators should inform the Sponsor that study drug has been temporarily interrupted. The data related to temporary interruption of study treatment will be documented in source documents and entered on the eCRF.

8.1.3. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, the investigator and the Sponsor CRP must agree whether continuing the study treatment is medically appropriate. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Participants will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
  - the investigator decides that the participants should be discontinued from the study
  - if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- subject decision
  - the participant requests to be withdrawn from the study

To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep participants in the study irrespective of the following:

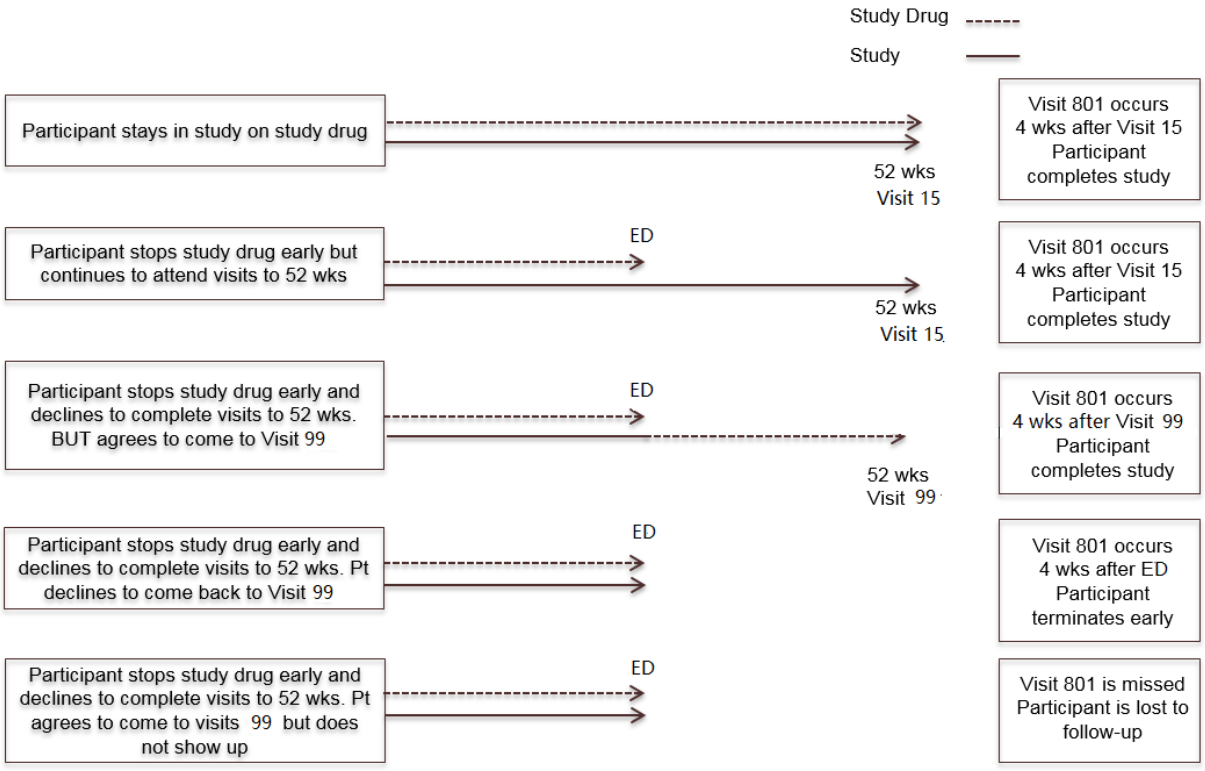
- adherence to or discontinuation from study drug
- adherence to visit schedule
- missing assessments
- study drug discontinuation due to AE
- development of comorbidities
- development of adverse clinical outcomes

The circumstances listed above are ***not*** valid reasons for discontinuation from the study.

Participants who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study.

Participants discontinuing from the study prematurely for any reason should complete adverse event and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2.1. Participant disposition and timing of safety follow-up for the primary endpoint (52 weeks)



Abbreviations: ED=early discontinuation; Pt= participant; wks=weeks

Figure GPIA.2. Illustration of participant disposition and safety follow-up for Clinical Protocol I8F-MC-GPIA.

8.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the participant will not be considered lost to follow-up.

Eli Lilly and Company personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 4.

9. Study Assessments and Procedures

Appendix 2 lists the laboratory tests that will be performed for this study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measurement in this study is the body weight. Body weight measurements will be collected at specific clinic visits as summarized in the Schedule of Activities (Section 2). Methods for measuring body weight are described in Appendix 8.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be collected at the times shown in the Schedule of Activities (Section 2) and analyzed in a manner controlled for type I error:

- Body weight (measuring method is described in Appendix 8)
- Waist circumference (measuring method is described in Appendix 8)
- HbA1c (%) (measured through central lab)
- Fasting glucose (mmol/L) (measured through central lab)
- Blood pressure (measuring method is described in Appendix 8)
- Fasting lipids (mmol/L) (measured through central lab)
- Fasting insulin (measured through central lab)

9.1.3. Patient-Reported Outcomes Assessments

The self reported questionnaires will be administered according to the Schedule of Activities (Section 2). At these visits, the questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff if the participant is not adversely affected by their fasting condition.

9.1.3.1. Short Form 36 version 2, acute, 1 week recall version

The SF 36v2 acute, 1 week recall version is a 36 item generic, patient-administered measure designed to assess the following 8 domains of health-related quality of life (HRQoL) “in the past week,” except for the Physical Functioning domain, which assesses an individual’s physical function in terms of how their health limits them “now” (i.e., currently):

• Physical Functioning

• Role Physical

• Bodily Pain

- General Health
- Vitality
- Social Functioning
- Role Emotional, and
- Mental Health

Information from these 8 domains are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths. Scoring of each domain and both summary scores are norm based and presented in the form of T scores, with a mean of 50 and standard deviation of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

9.1.3.2. Impact of Weight on Quality of Life Lite Clinical Trials Version

The IWQOL-Lite-CT is a 20-item, obesity-specific PRO instrument developed for use in obesity clinical trials. It assesses two primary domains of obesity-related HRQoL: physical (7 items), and psychosocial (13 items). A 5-item subset of the physical domain – the physical function composite is also supported. Items in the physical function composite describe physical impacts related to general and specific physical activities. All items are rated on either a 5-point frequency ("never" to "always") scale or a 5-point truth ("not at all true" to "completely true") scale. (Kolotkin et al. 2017, 2018).

9.1.3.3. EQ-5D-5L

Generic health-related quality of life will be assessed using the EQ-5D-5L (EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQoL Group 2015).

9.1.3.4. Patient Global Impression of Status for Physical Activity

Study participants will be asked to complete a Patient Global Impression of status (PGIS) item specifically developed for this study. This is a patient-rated assessment of current health limitation and is rated on a 5-point scale ranging from "1 not at all limited" to "5 extremely limited."

9.1.4. Appropriateness of Assessments

Efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with Obesity.

9.2. Adverse Events

All AEs will be collected from the signing of the ICF until the time points specified in the Schedule of Activities (Section 2).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open ended and non leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

The investigator will record all relevant AE and SAE information in the eCRF. After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Please refer to Appendix 6 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- when a condition related to the drug delivery system necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor per SAE-reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they

are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus. Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Event Monitoring with a Systematic Questionnaire

Patients with overweight and obesity are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at trial entry and monitored during the study for depression, suicidal ideation and behavior.

Baseline and treatment-emergent assessment of depression, suicidal ideation and behavior will be monitored during the study using the C-SSRS and PHQ-9 (Section 9.4.6).

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

The PHQ-9 is a validated self-report screening tool that assesses the presence and intensity of depressive symptoms. The PHQ-9, which incorporates the 9 Diagnostic and Statistical Manual-IV depression criteria “0” (not at all) to “3” (nearly every day), was developed for use in primary care settings (Kroenke et al. 2001).

Nonserious AEs obtained through the questionnaire are recorded and analyzed separately. Only *serious* AEs elicited through the C-SSRS or PHQ-9 are to be recorded as AEs via the eCRF and reported to Lilly or its designee within 24 hours as SAEs. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

9.2.3. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also product complaints:

- Deficiencies in labeling information, and
- Use errors for device or combination products due to ergonomic design elements of the product.

Sponsor collects product complaints on investigational products, medical devices, and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Complaints are also collected on comparators and other clinical trial material supplied, as required.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational drug, medical device, or drug delivery system so that the situation can be assessed.

As required by local regulations, and per instructions on the complaint form, the investigator will report to the sponsor and to their IRB/IEC any unanticipated adverse device effect or UADE (unanticipated problem that resulted in an SAE), or any device related product complaint that could have led to an SAE had precautions not been taken.

- For complaints associated with an SAE, report within 24 hours of site/trial personnel becoming aware of the product complaint.
- For any complaint that might have led to an SAE if appropriate action had not been taken, the intervention had not occurred, or circumstances had been less fortunate, report within 24 hours of site personnel becoming aware of the product complaint.
- For complaints not associated with an SAE, report within one business day of site/trial personnel becoming aware of the product complaint, or per the protocol.

9.2.4. Follow-up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 2).

9.3. Treatment of Overdose

Study drug overdose (more than the specified number of injections) will be reported as an AE. In the event of overdose, refer to the IB for tirzepatide.

9.4. Safety

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 2).

9.4.1. Electrocardiograms

For each participant, electrocardiograms (ECGs) should be collected according to the Schedule of Activities (Section 2) and Appendix 8.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, for immediate subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via the eCRF.

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements. The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

9.4.2. Vital Signs

For each participant, vital signs should be measured according to the Schedule of Activities (Section 2) and Appendix 8.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the participant receives the first dose of study treatment should be reported to Lilly or its designee as an AE via the eCRF.

9.4.3. Laboratory Tests

- For each participant, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).
- With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

- Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the participant receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Immunogenicity Assessments

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against tirzepatide as specified in the Schedule of Activities (Section 2).

At the visits and times specified in the Schedule of Activities (Section 2), blood samples will be collected to determine antibody production against tirzepatide. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken predose when applicable and possible. In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Appendix 6 (Hypersensitivity Events). Instructions for the collection and handling of blood samples will be provided by the sponsor. Sample collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post end of treatment).

Immunogenicity will be assessed by a validated assay designed to detect and titer antidrug antibody (ADA) in the presence of tirzepatide at a laboratory approved by the Sponsor. Samples with detected ADA will be tested for cross-reactive binding to native GIP and GLP-1. Antibodies may be further evaluated for their ability to neutralize the activity of tirzepatide. In vivo laboratory indicators for glycemic control (fasting blood glucose and HbA1c), effect on weight loss and PK will be utilized to detect potential neutralizing effect of ADA against tirzepatide.

Treatment-emergent antidrug antibodies are defined in Section 10.3.6.

ADA and hypersensitivity samples will be stored as per local regulation/EC requirement. Samples will be immediately destroyed once tirzepatide is launched for weight management indication or there is no further request on testing the samples from China authority.

9.4.5. Other Tests

9.4.5.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI and neurological systems, as well as a thyroid exam. Height, weight, and waist circumference will also be measured and recorded, per Appendix 8.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.6. Safety Monitoring

9.4.6.1. Hepatic Safety Monitoring

9.4.6.1.1. Close Hepatic Monitoring

Laboratory tests (Appendix 2), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of:	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST= aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

9.4.6.1.2. Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms*, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)

ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST= aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ration (PT-INR); tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computer tomography [CT] scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

9.4.6.1.3. Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the two consecutive blood tests should be at least 2 days.

9.4.6.2. Depression, Suicidal Ideation, and Behavior Risk Monitoring

Due to increased risk for depression (Luppino et al. 2010), suicidal ideation and behavior, participants with overweight and obesity will be screened at trial entry and monitored during the study for depression, suicidal ideation and behavior as explained in section 9.2.2.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases.

Baseline and treatment emergent assessment of depression, suicidal ideation and behavior will be monitored during the study using the C-SSRS and PHQ-9 (Section 9.2.2). Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment (Section 8.1).

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected from all randomized participants.

Plasma tirzepatide concentrations will only be determined from blood samples obtained from participants receiving tirzepatide treatment. Blood samples for PK assessment will be collected at times specified in the Study Schedule (Section 2). At each visit, one PK sample will be collected at fasting state before IP administration.

The date and time of the most recent tirzepatide SC injection administered prior to collecting the PK sample must be recorded on the eCRF from the study diaries.

The date and time at which each sample was drawn must be recorded on the laboratory accession page.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method.

Bioanalytical samples collected to measure tirzepatide concentration will be retained for a maximum of 1 year following last participant visit for the study..

9.6. Pharmacodynamics

Samples to assess the PD properties of tirzepatide are included in the efficacy measures and not applicable in this section.

9.7. Genetics

9.7.1. Whole Blood Sample[s] for Pharmacogenetic Research

Not Applicable.

9.8. Biomarkers

Not Applicable.

9.9. Health Economics

Health Economics and Medical Resource Utilization Parameters are not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 210 participants will be randomly assigned to study intervention (70 participants per intervention group).

The sample size determination assumes that evaluation of superiority of tirzepatide 10 mg and tirzepatide 15 mg to placebo will be conducted in parallel, each at a 2-sided significance level of 0.025 using a 2-sample t-test. Additionally, a difference of at least 11% mean body weight percentage reduction from randomization at 52 weeks for tirzepatide 10 mg and/or tirzepatide 15 mg compared with placebo, a common standard deviation (SD) of 11%, and a drop-out rate of 25% are assumed for statistical power calculations. Under the assumptions above, randomizing 210 participants in a 1:1:1 ratio to tirzepatide 10 mg (70), tirzepatide 15 mg (70), and placebo (70) provides more than 90% power to demonstrate superiority of each tirzepatide dose to placebo.

The chosen sample size and randomization ratio also provides >90% power to establish superiority of tirzepatide 10 mg and tirzepatide 15 mg doses to placebo in term of proportion of participants achieving at least 5% body weight reduction at 52 weeks, conducted in parallel using a Chi-square test, each at a 2-sided significance level of 0.025, assuming 25% placebo-treated participants and 90% tirzepatide-treated participants achieving the goal and a dropout rate of 25%.

10.1.1. Statistical Hypotheses

The alternative hypotheses for the primary objective are the following:

$H_{10,1}$: tirzepatide 10 mg QW is superior to placebo for percent change in body weight from randomization AND proportion of participants who achieve ≥5% body weight reduction at 52 weeks.

$H_{15,1}$: tirzepatide 15 mg QW is superior to placebo for percent change in body weight from randomization AND proportion of participants who achieve ≥5% body weight reduction at 52 weeks

The above two hypotheses will be tested in parallel, each at a 2-sided significance level of 0.025.

The alternative hypotheses for the key secondary objective controlling for type 1 error rate are the following:

$H_{10,2}$: tirzepatide 10 mg QW is superior to placebo for change in body weight (kg) from randomization at 20 weeks.

$H_{15,2}$: tirzepatide 15 mg QW is superior to placebo for change in body weight (kg) from randomization at 20 weeks.

$H_{10,3}$: tirzepatide 10 mg QW is superior to placebo for proportion of participants who achieve ≥10% body weight reduction at 52 weeks.

$H_{15,3}$: tirzepatide 15 mg QW is superior to placebo for proportion of participants who achieve ≥10% body weight reduction at 52 weeks.

$H_{10,4}$: tirzepatide 10 mg QW is superior to placebo for proportion of participants who achieve ≥15% body weight reduction at 52 weeks.

$H_{15,4}$: tirzepatide 15 mg QW is superior to placebo for proportion of participants who achieve ≥15% body weight reduction at 52 weeks.

$H_{10,5}$: tirzepatide 10 mg QW is superior to placebo for change from randomization in waist circumference (cm) at 52 weeks.

$H_{15,5}$: tirzepatide 15 mg QW is superior to placebo for change from randomization in waist circumference (cm) at 52 weeks.

The details of type I error rate control strategy for the above key secondary objectives will be provided in the statistical analysis plan (SAP).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table GPIA.4. Definition of population

Population	Description
Entered	All participants who sign informed consent.

Randomized	All participants who are randomly assigned a study treatment.
Modified Intent-to-Treat (mITT)	All randomly assigned participants who are exposed to at least 1 dose of study drug. Participants will be included in the treatment group they were randomized to.
Efficacy Analysis Set (EAS)	Data obtained during treatment period from mITT, excluding data after discontinuation of study drug (last dose date + 7 days).
Full analysis set (FAS)	Data obtained during treatment period from mITT, regardless of adherence to study drug.
Safety Analysis Set (SS)	Data obtained during the entire study from mITT, regardless of adherence to study drug.
Per Protocol Set (PPS)	Participants included in the randomized population who have completed Week 52 of study treatment without permanent discontinuation of IP and without significant protocol deviations through Week 52 that would significantly impact the primary objective. Treatment group will be defined on the basis of the treatment the participants actually receive.

Abbreviations: EAS = Efficacy Analysis Set, FAS = Full Analysis Set, IP = investigational product; mITT = Modified Intent-to-Treat, PPS = Per Protocol Set, SS = Safety Analysis Set.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report. Additional exploratory data analyses may be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided. In statistical summaries and analyses, data will be analyzed as randomized.

Unless specified otherwise, efficacy and safety will be assessed using the modified intention-to-treat (mITT) population, which consists of all randomized participants who are exposed to at least 1 dose of study drug. Baseline is defined as the last non-missing data collected at randomization (prior to first dosing of study drug). Unless specified otherwise, safety assessments will compare safety of tirzepatide doses with placebo irrespective of adherence to study drug. Thus, safety analysis will be conducted using safety analysis set (SS).

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time will be a mixed model for repeated measures (MMRM), with terms of treatment, visit, and treatment-by-visit interaction, stratification factors, and baseline measurement as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time, and cox proportional hazards regression analysis will be used to compare hazard rates among treatments.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Logistic regression will be used to examine the treatment difference in binary efficacy outcomes if there is a need to adjust for covariates. Otherwise, Fisher's exact test will be used to examine the treatment difference in categorical outcomes.

Summary statistics for discrete count measures will include sample size, mean, standard deviation (SD), median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures.

Other statistical methods may be used, as appropriate, and details will be described in the SAP.

10.3.2. Treatment Group Comparability

10.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. Of the mITT population, frequency counts and percentages of participants who completed the study, prematurely discontinued the study (and/or study drug), including reason for premature discontinuation, will be presented by treatment groups.

A Kaplan Meier analysis of time from randomization to premature discontinuation from study and discontinuation from study drug by treatment group will be provided.

10.3.2.2. Participant Characteristics

Demographics will be summarized by treatment group for all randomized participants.

10.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy, will be summarized by treatment arm for SS.

10.3.2.4. Treatment Compliance

Frequency counts and percentages of participants compliant to study drug will be summarized by treatment groups and visits for full analysis set (FAS).

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy analysis will be conducted using the efficacy analysis set (EAS). The primary analysis model will be a MMRM for body weight percent change over time and longitudinal logistic regression for proportion of participants achieving at least 5% body weight reduction over time. The response variable of MMRM will be the percent change in body

weight from baseline values obtained at each scheduled post baseline visit. The response variable of longitudinal logistic regression will be the proportion of participants achieving at least 5% body weight reduction at each scheduled post baseline visit. The independent variables of both analysis models are treatment group (tirzepatide 10 mg, tirzepatide 15 mg, and placebo), visit, and treatment-by-visit interaction, stratification factors, and baseline body weight as a covariate. An unstructured covariance structure will model relationship of within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Since the mean percent change in body weight and proportion of participants with ≥5% body weight reduction need to be achieved at the same time, no multiplicity adjustment is planned for these 2 tests.

10.3.3.2. Key Secondary Analyses

- superiority of each tirzepatide dose (10 mg and 15 mg) to placebo for change from randomization in change of body weight (kg) at 20 weeks visit
- superiority of each tirzepatide dose to placebo for the proportion of study participants who achieve ≥10% body weight reduction at 52 weeks visit
- superiority of each tirzepatide dose to placebo for the proportion of study participants who achieve ≥15% body weight reduction at 52 weeks visit
- superiority of each tirzepatide dose to placebo for change from randomization in waist circumference (cm) at 52 weeks visit

Additional details, including analysis methods for key secondary endpoints and the strategy for controlling overall type 1 error rate at a 2-sided alpha of 0.05 of primary and key secondary endpoint evaluation, will be provided in the SAP.

10.3.3.3. Tertiary/Exploratory Analyses

All exploratory efficacy analysis will be conducted using EAS. Details will be provided in the SAP.

10.3.4. Safety Analyses

Unless specified otherwise, safety assessments will compare safety of tirzepatide doses with placebo irrespective of adherence to study drug. Thus, safety analysis will be conducted using SS.

10.3.4.1. Study Drug Exposure

Exposure to each study treatment will be calculated for each participant and summarized by treatment group.

10.3.4.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Counts and proportions of participants experiencing events will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

The proportion of participants experiencing TEAE, SAE, discontinuation due to AE and DEATH will be summarized by treatment group.

10.3.4.3. Adverse Event of Special Interest

The following AEs are AEs of special interest (AESI) for this study:

- Severe hypoglycemia
- Major adverse cardiovascular events (adjudicated). Includes, but not limited to cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure.
- Treatment-Emergent Supraventricular arrhythmias and Cardiac Conduction Disorders
- Hepatobiliary disorders. Includes biliary colic, cholecystitis, and other gallbladder disease
- Severe GI events
- Acute renal events
- Major Depressive Disorder/Suicidal Behavior and Ideation
- Pancreatitis (adjudicated)
- C-Cell Hyperplasia and thyroid malignancies
- Allergic/Hypersensitivity Reactions, includes injection site reactions and ADA formation.

Summaries and analyses for incidence of AESIs will be provided by treatment. The details of analysis of AESI will be provided in SAP.

10.3.4.4. Other Adverse Event Assessments

10.3.4.4.1. Gastrointestinal Events

Summaries and analyses for incidence and severity of nausea, vomiting, and diarrhea will be provided by each treatment.

10.3.4.4.2. Events Related to Potential Abuse Liability

Two clusters of preferred terms for AEs suggestive of abuse liability will be analyzed. The first cluster includes Standardized MedDRA Queries (SMQ) of Drug abuse and dependence [20000101]. The second cluster is a Lilly Search Cluster "additional abuse potential" terms, which are additional terms suggestive of abuse liability that are not included in the SMQ Drug abuse and dependence [20000101].

Summaries and analyses for incidence of potential abuse liability terms will be provided by treatment. The details will be provided in SAP.

10.3.4.4.3. Depression, Suicidal Ideation, and Behavior

In addition to the summary of TEAEs, suicide-related events will be assessed by C-SSRS, and depression related symptoms will be assessed using PHQ-9.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the C-SSRS, will be listed by participant and visit.

The PHQ-9 total score will be summarized by treatment groups.

The analysis details will be provided in the SAP.

10.3.4.4.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual values and change from randomization to post-randomization values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. Change from randomization to post-randomization value will be summarized for participants who have both a randomization and at least 1 post randomization result.

The percentages of participants with treatment-emergent abnormal, high, or low measures (including laboratory, vital, and ECG parameters) at any time will be summarized and compared between treatment groups using Fisher's exact test.

The analysis details will be provided in SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

All plasma tirzepatide concentration-time data will be pooled and evaluated using conventional methods. Details about the analyses to be conducted will be contained in the PK/PD analysis plan.

10.3.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with treatment-emergent (TE) ADA+ to tirzepatide will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA), or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA+ participants the distribution of maximum titers will be described. The frequency of ADA cross-reactive to endogenous counterparts (native GIP and GlP-1) maybe tabulated in TE ADA+ participants.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to tirzepatide may be assessed.

10.3.7. Other Analyses

10.3.7.1. Patient Reported Outcomes

Analyses of actual and change from baseline in the participant reported health outcomes in EAS will be conducted using an analysis of covariance (ANCOVA). The details on questionnaire-specific analyses will be provided in the SAP.

10.3.7.2. Subgroup Analyses

Details of the subgroup analyses will be shown in the SAP.

The following subgroup variables will be considered (but not limited to):

- Age (<65 years and ≥65 years);
- Sex (female and male)
- Baseline BMI (<28, ≥28)

The outcome measures for the subgroup analyses will include:

- percent change in body weight from randomization at 52 weeks
- proportion of participants achieving at least 5% body weight reduction at 52 weeks

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
BP	blood pressure
CHF	congestive heart failure
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease-Epidemiology
CIOMS	Council for International Organizations of Medical Sciences
CMV	Cytomegalovirus
complaint	A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also product complaints: a. Deficiencies in labeling information, and b. Use errors for device or combination products due to ergonomic design elements of the product.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.

CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
D.Bil	direct bilirubin
DBP	diastolic blood pressure
DPP-4	dipeptidyl-peptidase-4
EAS	efficacy analysis set
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ED	early discontinuation
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ERCP	endoscopic retrograde cholangiopancreatography
FAS	full analysis set
FSG	fasting serum glucose
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GHO	Global Health Observatory

GI	Gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HDV	hepatitis D virus
HR	heart rate
HRT	hormonal replacement therapy
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
INR	international normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB/IEC	Institutional Review Boards /Independent Ethics Committees
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite-Clinical trials
IWRS	interactive voice-response system/interactive web-response system
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
Medical device incident	A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to a serious injury, death of a participant/user/other person, or to a serious deterioration in his/her state of health.
MEN	Multiple endocrine neoplasia
MH	Mental Health domain
MHP	Mental Health Professional
mITT	modified intentto-treat
MMRM	mixed-model for repeated measures
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
NYHA	New York Heart Association
PC	Product Complaints
PCOS	polycystic ovary syndrome
PGIS	Patient Global Impression of status
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
PPS	per protocol set
PROs	patient-reported outcomes
PT	prothrombin Time
QW	once weekly
RE	Role-Emotional domain

RP	Role-Physical domain
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	Subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SF-36 v2 acute form	Short-Form-36 Health Survey (SF-36), version 2
SMQ	Standardized MedDRA Queries
SS	Safety analysis set
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	treatment emergent
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TSH	thyroid stimulating hormone
TxP	treatment period
TZP	Tirzepatide
UADE	unanticipated problem that resulted in an SAE
ULN	upper limit of normal
VAS	visual analogue scale
VLDL	very low density lipoprotein
VT	Vitality domain

WHO	World health organization
wks	weeks

Appendix 2. Clinical Laboratory Tests

- The tests detailed below will be performed by a central lab unless designed as local in the schedule of activities (Section 2) and in the table below.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing (Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.)
- Investigators must document their review of each laboratory safety report.
- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
	Bicarbonate
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
	Alkaline phosphatase (ALP)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose
Urine Chemistries[a]	Albumin
Albumin	Creatine kinase (CK)
Creatinine	
	Hormones (females)
	Pregnancy Test[a] serum and/or urine (local)[b]
	Follicle-stimulating hormone[a,d]
	Calculations[a]
	eGFR (calculated by CKD-EPI equation)[c]
	Urine microalbumin/creatinine ratio
Cystatin-C[a]	
	Pancreas (exocrine) [a]
HbA1c[a]	Pancreatic amylase
	Lipase
Endocrine[a]	
Calcitonin[a]	**Immunogenicity**[a,e]
Thyroid-stimulating hormone (TSH)[a]	Tirzepatide anti-drug antibody
	Pharmacokinetic Sample
	Lipid Panel[a]
	Total cholesterol
Insulin[a]	LDL-C
	HDL-C
C-peptide[a]	VLDL
	Triglycerides
Free Fatty Acids[a]	

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PK = pharmacokinetics; RBC = red blood cells; VLDL = very low-density lipoprotein; WBC = white blood cells.

[a] All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

[b] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.
A local urine pregnancy test must be performed at Visit 2 with the result available prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests (beyond those required per the Schedule of Activities [Section 2]) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation. For sites which can't perform local urine pregnancy test, a local serum pregnancy test can be performed instead.

[c] Estimated glomerular filtration rate will be calculated by the central laboratory and included in laboratory result reports.

[d] Follicle-stimulating hormone test performed at Visit 1 for postmenopausal women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for at least 12 months without an alternative medical cause.

[e] Results will not be provided to the investigative sites.

Appendix 3. Laboratory Assessments for Hypersensitivity Events

Guidance for laboratory assessments for hypersensitivity events

- Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected
- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

The following table summarizes the laboratory tests for hypersensitivity events. These laboratory tests are bundled in the hypersensitivity laboratory testing kit.

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
Tirzepatide anti-drug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tirzepatide concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. Note: If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine sample for N-methylhistamine testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine Nmethylhistamine testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for Nmethylhistamine testing at the next regularly scheduled visit or after 4 weeks, whichever is later.
N-methylhistamine	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Complement (C3, C3a, and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel (IL-6, IL-1β, IL-10)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: ADA = anti-drug antibody; PK = pharmacokinetic.

Appendix 4. Study Governance Considerations

Appendix 4.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 4.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the participants understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each participant or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the participants may have throughout the study and sharing in a timely manner any new information that may be relevant to the participant's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 4.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for participants. Individual investigators may have additional local requirements or processes.

Appendix 4.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 4.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 4.1.5. Investigator Information

Physicians with a specialty in endocrinology, cardiology, nephrology, internal medicine, family medicine, general medicine, or any other qualified physician with clinical research experience will participate as investigators in this clinical trial.

Appendix 4.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 4.1.7. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified participants will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 4.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will provide instruction on the protocol, the completion of the electronic case report forms (eCRFs), and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax, and
- review and verify data reported to detect potential errors.

In addition, Lilly or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 4.2.1. Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data (scales, self-reported diary data) will be collected by the subject/investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 4.3. Study and Site Closure

Appendix 4.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4.4. Publication Policy

- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The publication policy for Study I8F-MC-GPIA is described in the Clinical Trial Agreement.

Appendix 4.5. Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable will not be transferred.
- The participant must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Appendix 4.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Appendix 5. Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 9.4.6.1 for guidance on appropriate test selection.

- The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.
- Local testing may be performed in addition to central testing when necessary for immediate patient management.
- Results will be reported if a validated test or calculation is available.

Hematology

Hemoglobin

Hematocrit

Erythrocytes (RBCs - Red Blood Cells)

Leukocytes (WBCs - White Blood Cells)

Differential:

- Neutrophils, segmented
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

Platelets

Cell morphology (RBC and WBC)

Coagulation

Prothrombin Time, international normalized ratio (PT-INR)

Serology

Hepatitis A Virus (HAV) Testing:

- HAV Total Antibody
- HAV IgM Antibody

Hepatis B Virus (HBV) Testing:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B surface antibody (anti-HBs)
- Hepatitis B core total antibody (anti-HBc)

Clinical Chemistry

Total bilirubin

Direct bilirubin

Alkaline phosphatase (ALP)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Gamma-glutamyl transferase (GGT)

Creatine kinase (CK)

Other Chemistry

Acetaminophen

Acetaminophen protein adducts

Alkaline phosphatase isoenzymes

Ceruloplasmin

Copper

Ethyl Alcohol (EtOH)

Haptoglobin

Immunoglobulin IgA (quantitative)

Immunoglobulin IgG (quantitative)

Immunoglobulin IgM (quantitative)

Phosphatidylethanol (PEth)

Urine Chemistry

Drug Screen

Ethyl glucuronide (EtG)

Other Serology

Hepatitis B core IgM antibody

Hepatitis B core IgG antibody

HBV DNA [d]

Hepatis C Virus (HCV) Testing:

HCV antibody

HCV RNA [d]

Hepatitis D Virus (HDV) Testing:

HDV antibody

Hepatitis E Virus (HEV) Testing:

HEV IgG antibody

HEV IgM antibody

HEV RNA [d]

Microbiology [c]

Culture:

Blood

Urine

Anti-nuclear antibody (ANA)

Anti-smooth muscle antibody (ASMA) [a]

Anti-actin antibody [b]

Epstein-Barr Virus (EBV) Testing:

EBV antibody

EBV DNA [d]

Cytomegalovirus (CMV) Testing:

CMV antibody

CMV DNA [d]

Herpes Simplex Virus (HSV) Testing:

HSV (Type 1 and 2) antibody

HSV (Type 1 and 2) DNA [d]

Liver Kidney Microsomal Type 1 (LKM-1) Antibody

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Assayed ONLY by Investigator-designated local laboratory ONLY; no central testing available.
[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

Appendix 6. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

Appendix 6.1. Special Safety Topics

Appendix 6.1.1. Hypoglycemia

Upon informed consent form (ICF) signing, all participants will be educated about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia.

Hypoglycemia may be identified by spontaneous reporting of symptoms from participants (whether confirmed or unconfirmed by simultaneous glucose values) or by blood glucose (BG) samples collected during study visits. All participants who develop T2DM during the study will be provided with glucometers. Participants without diabetes may, at the investigator's discretion, be given glucometers to assist in the evaluation of reported symptoms consistent with hypoglycemia. Participants receiving glucometers will be provided a diary to record relevant information (for example, glucose values, symptoms).

Hypoglycemic episodes will be recorded on a specific electronic case report form (eCRF) and should not be recorded as adverse events (AEs) unless the event meets serious criteria. If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE and serious AE (SAE) eCRFs, and reported to Lilly as an SAE.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the plasma glucose [PG] values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2019 American Diabetes Association position statement on glycemic targets (American Diabetes Association 2019a):

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of <70 mg/dL (<3.9 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG <70 mg/dL (<3.9 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG <70 mg/dL (<3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (<3.0 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured BG <54 mg/dL (<3.0 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available but with a measured BG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

To avoid duplicate reporting, all consecutive BG values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

Appendix 6.1.2. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases) (Banks and Freeman 2006; Koizumi et al. 2006); the pain is often associated with nausea and vomiting);
- serum amylase (total and/or pancreatic) and/or lipase ≥3x upper limit of normal (ULN)
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with tirzepatide, but will

continue in the study. A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each participant will have measurements of p-amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 2) to assess the effects of the investigational doses of tirzepatide on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzynemia (lipase and/or pancreatic amylase ≥3x ULN) is not mandated, but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition. Only cases of pancreatic hyperenzynemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from participants with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

Appendix 6.1.3. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of medullary thyroid carcinoma (MTC) and/or Multiple Endocrine Neoplasia syndrome type 2 (MEN-2) will be excluded from the study. Participants are diagnosed with MTC and/or MEN-2 during the study will have study drug stopped and should continue follow-up with an endocrinologist.

The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy (including MTC and papillary carcinoma) and measurements of calcitonin. This data will be captured in specific eCRFs. The purpose of calcitonin measurements is to assess the potential of tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Appendix 6.1.4. Calcitonin Measurements

If an increased calcitonin value (see definitions below) is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped and calcitonin levels should be measured after an appropriate washout period.

For participants who require additional endocrine assessment because of increased calcitonin concentration as defined in this section, data from the follow-up assessment will be collected in the specific section of the eCRF.

Calcitonin Measurements in Participants with eGFR ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 is defined below. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

- *calcitonin value ≥20* ng/L *and <35* ng/L *AND ≥50% increase from the screening value.* These participants will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the study drug should be stopped, and the participant encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.
- *calcitonin value ≥35* ng/L *AND ≥50% over the screening value*. In these participants, study drug should be stopped, and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

Calcitonin Measurement in Participants with eGFR <60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a *calcitonin value ≥35* ng/L *AND ≥50% over the screening value.* If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

In these participants, study drug should be discontinued (after first confirming the value) and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

Appendix 6.1.5. Major Adverse Cardiovascular Events

Deaths and nonfatal cardiovascular AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. The nonfatal cardiovascular AEs to be adjudicated include

- myocardial infarction
- hospitalization for unstable angina
- hospitalization for heart failure
- coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

Appendix 6.1.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis

should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 9.2 must be reported as SAEs.

Appendix 6.1.7. Hypersensitivity Events

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 3. Laboratory results are provided to the sponsor via the central laboratory.

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug(s). Study drug(s) may be restarted when/if it is safe to do so, in the opinion of the investigator.

Appendix 6.1.8. Injection Site Reactions

Injection site reactions will be collected on the eCRF separate from the hypersensitivity reaction eCRF. At the time of AE occurrence, samples may be collected if possible for measurement of tirzepatide antidrug antibody (ADA) and tirzepatide concentration.

Appendix 6.1.9. Antidrug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 9.4.4.

Appendix 6.1.10. Hepatobiliary Disorders

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.

Appendix 6.1.11. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe gastrointestinal (GI) AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 7.4.2.

Appendix 6.1.12. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. Gastrointestinal AEs have been reported with tirzepatide, including nausea, diarrhea, and vomiting. This is consistent with other glucagon-like peptide-1 receptor (GLP-1R) agonists (Aroda and Ratner

2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

Appendix 6.1.13. Depression, Suicidal Ideation or Behavior Monitoring

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Patient Health Questionnaire-9 (PHQ-9). Participants will be referred to a Mental Health Professional (MHP) if in the opinion of the investigator it is necessary for the safety of the participant or if the participant had any of the following:

- a PHQ-9 score ≥ 15
- C-SSRS responses of
    - A "yes" answer to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan)
      or
    - A "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS
      or
    - A "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS.

Appendix 7. Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential:
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (for example; amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered woman of childbearing potential:

Article I. Premenarchal

Article II. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (for example; mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Article III. Postmenopausal female

- A postmenopausal state is defined as either
  - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone (FSH) $\geqslant$40 mIU/mL; or
  - A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
  - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance
Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Two forms of effective contraception, where at least 1 form is highly effective, will be used. Effective contraception may be used as the second therapy. Barrier protection methods without

concomitant use of a spermicide are not a reliable or acceptable method. The use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle), and agrees to maintain this status throughout trial follow-up.

Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception

- Vasectomy – for men in clinical studies

Note: Implantable contraceptives and injectable contraceptives (such as Depo-Provera®) are only permitted if started more than 18 months prior to screening. Participants should not start these methods of contraception after being enrolled in the study.

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Men, regardless of their fertility status, with nonpregnant women of child-bearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for 5 half-lives of study drug plus 90 days, which is approximately 4 months after the last injection. Periodic abstinence (for example, calendar, ovulation, symptothermal, and postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential.

Men who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with females (usual lifestyle). In these situations, men are not required to use contraception.

Men should refrain from sperm donation for the duration of the study and for 5 half-lives of study drug plus 90 days after the last dose of study drug, corresponding to 4 months after the last injection.

Collection of Pregnancy Information

Male participants with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 9.2.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Appendix 8. Protocol GPIA Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, Vital Signs and Electrocardiogram

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2008)

Measuring Height

Step 1. Ask the participant to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when their height is measured).

Step 2. Ask the participant to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the backboard, the stadiometer or the wall.

Step 3. Ask the participant to look straight ahead without tilting their head up.

Step 4. Ask the participant to breathe in and stand tall. Measure and record the participant's height in centimeters (cm) to 1 decimal place.

Measuring Weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms (kg) to one decimal place.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Body weight must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

Step 1. Ask the participant to remove their footwear, outerwear (coat, jacket, etc.), any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when weight is measured).

Step 2. Make sure the scale is placed on a firm, flat, even surface (not on carpet, on a sloping surface, or a rough, uneven surface).

Step 3. Ask the participant to step onto the scale with 1 foot on each side of the scale.

Step 4. Ask the participant to stand still with arms by sides and then record weight in kilograms (kg) to the nearest one-tenth kg.

Measuring Waist Circumference

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken at the end of a normal expiration using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.
- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the eCRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1: Ask the participant to wear light clothing (if available, patient gowns could also be used).

Step 2: Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.

Step 3: Ask the participant to relax and measure the participant's waste circumference.

Vital Sign Measurements (blood pressure and heart rate)

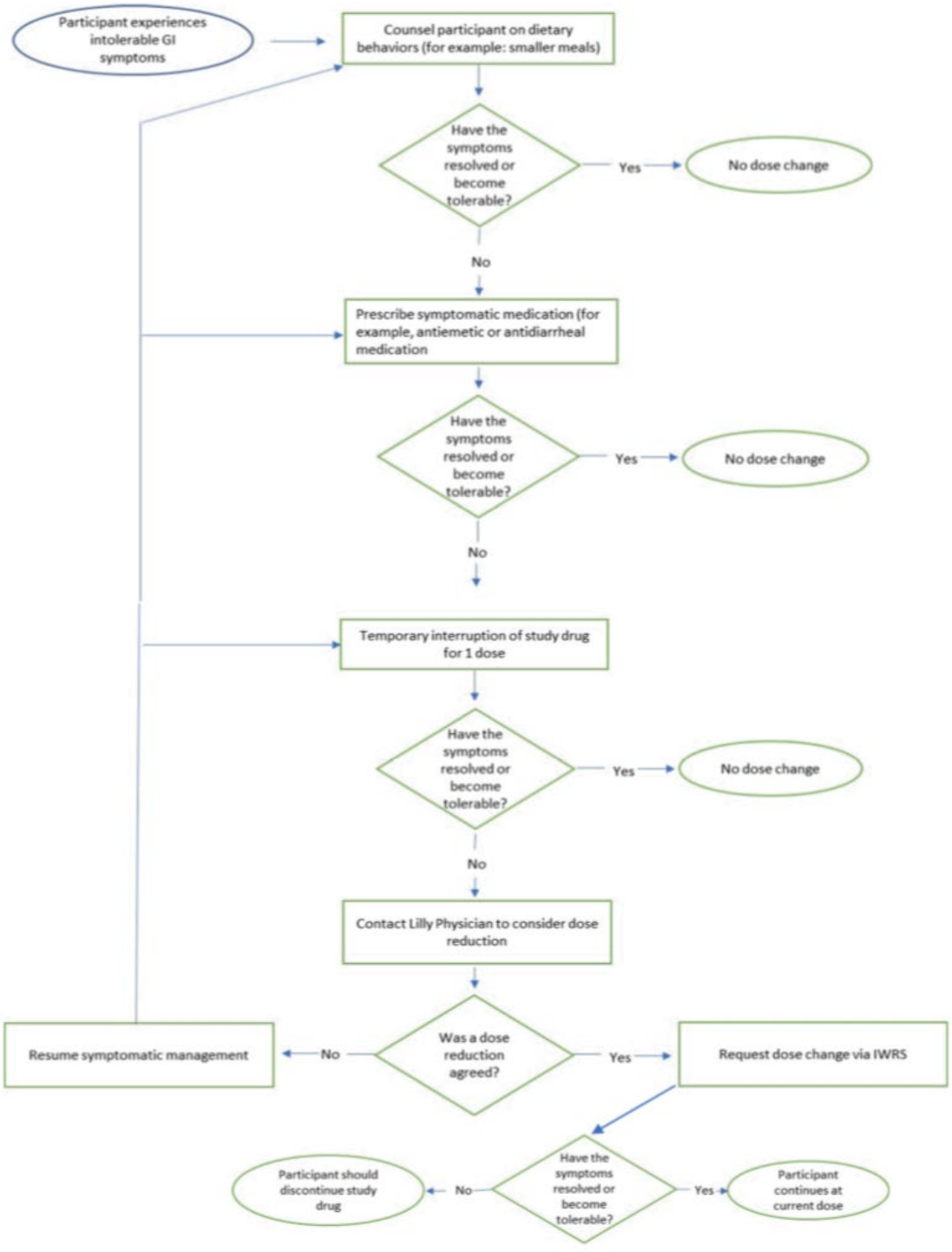
- Vital sign measurements (blood pressure and heart rate, measured by pulse) should be taken before obtaining an electrocardiogram (ECG) tracing and before collection of blood samples for laboratory testing
- The participant should sit quietly for 5 minutes before vital signs measurements are taken
- For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and BP needs to be recorded in the electronic case report form (eCRF)
- Blood pressure must be taken with an automated blood pressure instrument.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

Note: In the event pulse measurement cannot be taken via an automated blood pressure instrument, the preferred location for measurement of pulse is the radial artery.

Electrocardiogram

- All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory.
- 12-lead ECGs should be obtained after the participant has rested in a supine position for at least 10 minutes.
- Electrocardiograms should be collected at least 30 minutes prior to collection of blood samples for laboratory testing, including PK samples.

Appendix 9. Management of Gastrointestinal Symptoms



Abbreviations: GI = gastrointestinal; IWRS = interactive web-response system.

Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

The Sponsor and study investigators will notify Ethical Review Boards (ERBs) as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as early as possible following implementation.

After approval by local ERBs, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits,"

- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

> **Telemedicine:** Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, review study participant diary (including study drug compliance), review diet and exercise goals, Columbia-Suicide Severity Rating Scale (C-SSRS, Since Last Visit Version), Self-Harm Supplement Form, Self-Harm Follow-up Form (if applicable), and Patient Health Questionnaire 9 (PHQ-9).

Data capture

In source documents and the case report form (CRF), the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, serious adverse events (SAEs), and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for hypersensitivity, immunogenicity and pharmacokinetic analyses as described in Section 9.4.4 and Appendix 3. The local laboratory must be qualified in accordance with applicable local regulations. Clinically significant laboratory findings that meet the definition of an adverse event must be recorded in the AE eCRF.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, minimize missing data, and preserve the intended conduct of the study, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	**Tolerance**
Visit 15 or Visit 99	The visit window may be brought forward within 14 days before the intended date, or extended up to 28 days after the intended date, upon specific guidance from the Sponsor.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Appendix 11. Protocol Amendment [I8F-MC-GPIA(a)] Summary [Efficacy and Safety of Tirzepatide Once Weekly in Chinese Participants without Type 2 Diabetes Who Have Obesity or are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-CN)]

Overview

Protocol I8F-MC-GPIA(a) titled "Efficacy and Safety of Tirzepatide Once Weekly in Chinese Participants without Type 2 Diabetes Who Have Obesity or are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-CN)" has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I8F-MC-GPIA Amendment (a)

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities	Added an activity entitled "register study visit in IWRS"	Activity was added to ensure all visits are registered, which allows monitoring of study activities using IWRS reports timely.
2. Schedule of Activities	Added a sentence to footnote v "The Self-Harm Supplement Form is only required if responses to the C-SSRS indicate that the patient needs to be further evaluated for self-harm risk." Revised the wording in footnote w "Self-Harm forms will be completed by participants" to "Self-Harm forms will be completed by investigators".	Footnote v was revised to provide a clear instruction on the condition of completing Self-Harm forms. Footnote w was revised to correct the error in the original protocol.
2. Schedule of Activities and 5.1.1.2.2 Treatment Period	Removed activities for hand out diary at Visit 15 and Visit 99.	The activities were removed to correct errors in the original protocol.
7.1 Treatment Administered	Added a footnote to Table GPIA.3 Treatment regimen.	The footnote was added to provide a clear instruction on Tirzepatide dose escalation.

7.4.2 Management of Participants with Gastrointestinal Symptoms	Revised the sentence "for example, 15 mg reduced to 10 mg or 10 mg reduced to placebo" to "for example, 15 mg and 12.5 mg reduced to 10 mg, 10 mg or lower reduced to placebo, the lower dose will be maintained for the rest of the study, with no re-escalation allowed"	The wording was rephrased to provide a more clear instruction on dose reduction.
9.4.6.1 Hepatic Safety Monitoring	For participants with baseline total bilirubin (TBL)≥1.5x upper limit of normal (ULN), close hepatic monitoring evaluation was changed to "TBL≥1.5xbaseline", while comprehensive hepatic evaluation was changed to "TBL≥2xbaseline".	The evaluations were changed to correct the errors in original protocol, and be consistent with global patient safety standard language.
Appendix 7. Contraceptive Guidance and Collection of Pregnancy Information	Note regarding follicle stimulating hormone levels used to confirm a postmenopausal state in women has been deleted.	The note could lead to misinterpretation of inclusion criterion 4.
Appendix 7. Contraceptive Guidance and Collection of Pregnancy Information	Added text "started more than"	The sentence was revised to maintain consisitency with the text from the exclusion criteria.
Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstance	An appendix describing mitigation for exceptional circumstances was added as Appendix 10.	Language was added to address exceptional circumstances due to unforeseen widespread emergencies (such as pandemics or natural disasters).

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all participants enrolled in Study GPIA. However, for those participants whose participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 10 for additional guidance.

Table GPIA.1. Schedule of Activities

Visit[a]	**1**	**2[b]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**99[c]**	**ED[d]**	**801[e]**
Week of Treatment	**-2**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**52**		**4 wks Post TxP**
Allowable Deviation (days)[f]		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**		**±7**
Fasting (>8 hours) Visit[a]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		**X**		**X**	**X**	**X**	**X**
Telephone Visit									**X**	**X**		**X**		**X**				
Informed consent	X																	
Randomization		X																
Register study visit in IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessment																		
Medical history[g]	X																	
Physical examination	X																	
Height	X																	
Weight[h]	X	X	X	X	X	X	X	X			X		X		X	X	X	X
Waist circumference		X	X	X	X	X	X	X			X		X		X	X	X	X
Electrocardiogram[i]		X		X		X					X				X		X	X
Vital signs (3 sitting BP and HR)[j]	X	X	X	X	X	X	X	X			X		X		X		X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Education and Assessment																		
Hand out diary, instruct in use[k]		X	X	X	X	X	X	X			X		X		~~X~~	~~X~~		

[v] The C-SSRS, Self-Harm Supplement Form and PHQ-9 should be administered *after* assessment of adverse events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed. The C-SSRS questionnaire will be completed by ~~site staff~~investigators, while PHQ-9 will be completed by participants. The Self-Harm Supplement Form is only required if responses to the C-SSRS indicate that the patient needs to be further evaluated for self-harm risk.

[w] Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form, per instructions in the form. Self-Harm forms will be completed by ~~participants~~investigators.

5.1.1.2.2. Treatment Period

Visit 99

Participants should attend this visit in the fasting state. Procedures to be completed are:

- measurement of weight and waist circumference
- listing of concomitant medications
- urine pregnancy test
- ~~hand out diary and instruct in use~~
- assessment of AEs, and
- completion of the mental health questionnaires (after the AE assessment)

7.1 Treatments Administered

This study involves a comparison of 10 mg and 15 mg tirzepatide administered by subcutaneous injection once weekly with placebo. Table GPIA.3 shows the treatment regimens.

Table GPIA.3. Treatment Regimens

ARM Name	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
Dose[a]	10 mg QW	15 mg QW	N/A
Route of Administration	SC	SC	SC
Sourcing	Provided centrally by the Sponsor and dispensed via IWRS		

Abbreviations: IWRS = interactive web response service; N/A= not available, QW= once-weekly, SC= subcutaneous

[a] Tirzepatide treatment will follow a fixed dose escalation that initiated at 2.5 mg QW for 4 weeks and increased by 2.5 mg every 4 weeks (2.5 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the desired dose is achieved and maintained for the duration of the study.

7.4.2. Management of Participants with Gastrointestinal Symptoms

Participants who experience intolerable GI symptoms (for example: nausea, vomiting, or diarrhea) at any time during the study, should first be counselled on dietary behaviors that may help mitigate nausea and vomiting, (for example, eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, and stopping eating when they feel full). If symptoms persist, the participant should be prescribed, at the investigator's discretion, symptomatic medication (for example, antiemetic or antidiarrheal medication). A temporary interruption of study drug for 1 dose is permitted, provided the participant has taken the last 3 weekly doses. Study treatment should be resumed at the assigned dose immediately, either alone or in combination with

symptomatic medication (Appendix 9). Management of study drug after interruptions >1 dose is discussed in Section 8.1.2.

If intolerable GI symptoms (for example, nausea, vomiting, or diarrhea) persist despite the above measures, the investigator should contact Lilly to consider reinitiating study drug at the next lowest maintenance dose in a blinded fashion (for example, 15 mg and 12.5 mg reduced to 10 mg, ~~or~~ 10 mg or lower reduced to placebo, the lower dose will be maintained for the rest of the study, with no re-escalation allowed).

9.4.6.1. Hepatic Safety Monitoring

9.4.6.1.1. Close Hepatic Monitoring

Laboratory tests (Appendix 2), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of:	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5~~2~~x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST= aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

9.4.6.1.2. Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms*, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2~~1.5~~x baseline (except for patients with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.
Abbreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST= aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

Appendix 7. Contraceptive Guidance and Collection of Pregnancy Information

Women in the following categories are not considered woman of childbearing potential:

Article I. Premenarchal

Article II. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (for example; mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Article III. Postmenopausal female

- A postmenopausal state is defined as either
    - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone (FSH) ⩾40 mIU/mL; or
    - A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
    - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

~~***Note***: A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement (⩾40 mIU/mL) is required.~~

- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)

- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle), and agrees to maintain this status throughout trial follow-up.

Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception

- Vasectomy – for men in clinical studies

Note: Implantable contraceptives and injectable contraceptives (such as Depo-Provera®) are only permitted if started more than 18 months prior to screening. Participants should not start these methods of contraception after being enrolled in the study.

Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstance

The whole Appendix 10 section is newly added into this protocol.

Leo Document ID = 194eb6d3-bf51-4d5b-8879-a45be036ac96

Approver: PPD

Approval Date & Time: 25-Aug-2021 04:09:38 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 25-Aug-2021 20:06:16 GMT

Signature meaning: Approved